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RENAL REPLACEMENT THERAPY IN THE CRITICALLY ILL

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ACADEMIC DISSERTATION

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LIST OF ORIGINAL PUBLICATIONS

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I Vaara S, Pettilä V, Kaukonen KM: Quality of pharmacokinetic studies in critically ill patients receiving continuous renal replacement therapy. *Acta Anaesthesiol Scand* 56:147-157, 2012.

II Vaara ST, Pettilä V, Reinikainen M, Kaukonen KM, for the Finnish Intensive Care Consortium. Population-based incidence, mortality and quality of life in critically ill patients treated with renal replacement therapy – A nationwide retrospective cohort study in Finnish ICU's. *Crit Care* 2012 16:R13, 2012.

III Vaara ST, Reinikainen M, Kaukonen KM, Pettilä V, for the Finnish Intensive Care Consortium. Association of ICU size and annual case volume of renal replacement therapy patients with mortality. *Acta Anaesthesiol Scand* 56:1175-1182, 2012.

IV Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, Laurila JJ, Mildh L, Reinikainen M, Lund V, Parviainen I, Pettilä V, the FINNAKI study group. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy - Data from the prospective FINNAKI study. *Crit Care* 16:R197, 2012.

LIST OF ABBREVIATIONS

AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
APACHE	Acute Physiology and Chronic Health Evaluation
ATN study	VA/NIH Acute Renal Failure Trial Network (ATN) Study
AUC	area under the (receiver-operator characteristic) curve
BEST study	Beginning and Ending Supportive Therapy for the Kidney - study
CrCl	Creatinine clearance
CRRT	Continuous renal replacement therapy
CVVH	Continuous venovenous hemofiltration
CVVHD	Continuous venovenous hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
ESRD	End-stage renal disease
EQ-5D index	EuroQol-instrument for analysing health-related quality of life
GFR	Glomerular filtration rate
HRQOL	Health-related quality of life
ICD-10	International Classification of Diseases, 10th revision
ICU	Intensive care unit
IHD	Intermittent hemodialysis
IRRT	Intermittent renal replacement therapy
KDIGO	Kidney Disease: Improving Global Outcomes
LMWH	Low-molecular-weight heparin
MARS	Molecular absorbent recirculating system
MDRD	Modification of Diet in Renal Disease
NGAL	Neutrophil gelatinase-associated lipocalin
RCT	Randomized controlled trial
RENAL study	The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study
RIFLE	Risk, Injury, Failure, Loss, End-stage disease –classification
RRT	Renal replacement therapy
SAPS	Simplified Acute Physiology Score
SMR	Standardized mortality ratio
SOFA	Sequential Organ Failure Assessment
TISS	Therapeutic Intervention Scoring System
UF	Ultrafiltration
VAS	Visual analogue scale
Vd	Volume of distribution

ABSTRACT

Aims

The objectives of this study were to evaluate the incidence and outcome of critically ill patients receiving renal replacement therapy (RRT) for acute kidney injury (AKI), and to assess factors associated with outcome. The practices to provide RRT in Finnish intensive care units (ICUs) were described. Additionally, the quality of published pharmacokinetic studies in patients with continuous RRT (CRRT) was studied.

Materials and methods

Study I was a systematic literature review including 49 original publications that reported the pharmacokinetic results of adult critically ill patients receiving CRRT. The general quality of the studies was assessed with the Downs and Black Index score, and the adequacy of the reporting of the CRRT-related parameters was assessed with the Acute Dialysis Quality Initiative minimal reporting criteria.

Altogether 25 200 patients were included in studies II-IV. Data on all admissions in the 24 member-ICUs of the Finnish Intensive Care Consortium between 2007 and 2008 were obtained and included in the incidence calculations. Of the 24 904 patients included in study II, 1686 received RRT for AKI. Their hospital and 6-month mortality and health-related quality of life (HRQOL) were compared to the 23 218 patients without RRT. In study III, 1558 RRT-treated patients from the same dataset were divided according to treatment in 1) small or large ICUs and 2) ICUs classified into tertiles according to annual case volume of RRT-treated patients. The crude and adjusted mortality rates were compared in these groups. Study IV was part of the prospective, observational, FINNAKI cohort study, conducted in 17 Finnish ICUs during a five-month period. The data of 296 RRT-treated patients were used to analyze characteristics of the RRT and factors associated with 90-day mortality with special emphasis on fluid balance prior to RRT initiation.

Main results

The general quality of pharmacokinetic studies on CRRT-receiving patients was moderate. The reporting of CRRT and patient characteristics was poor according to the criteria by Acute Dialysis Quality Initiative, while the retrospectively calculated CRRT dose in these studies was mainly according to the recommendations.

In study II, the population-based incidence of RRT for AKI was 20.2 per 100 000 adults per year. The hospital mortality of RRT-treated patients was 35.0% and the 6-month mortality was 49.4%. Patients with RRT perceived their HRQOL to be as good as those without at six months. In study III, patients treated in small ICUs had higher crude and adjusted hospital mortality rates compared to those treated in large ICUs. In study IV, the 90-day mortality of RRT-treated patients was 39.2%. Patients with fluid overload at RRT initiation had twice as high crude 90-day mortality rate than patients without, and the difference remained after adjusting for patient age, severity of illness, presence of sepsis, time from ICU admission to RRT initiation, and initial RRT modality. RRT was initiated after a median of 14 hours from ICU admission in the presence of a

median of three indications. In 73% of patients, the initial RRT modality was continuous. The CRRT dose adjusted for daily duration of treatment was 27.9 mL/kg/h.

Conclusions

The reporting of CRRT-related parameters in pharmacokinetic studies was inadequate. The hospital, 90-day, and 6-month mortality rates of patients with RRT for AKI were high compared to other ICU-treated syndromes, but lower than previously reported for patients with RRT. Patients treated in small central hospitals demonstrated higher crude and adjusted hospital mortality rates compared to those treated in larger hospitals. Fluid overload at RRT initiation was associated with an increased risk for 90-day mortality. RRT was initiated early after ICU admission.

Keywords

acute kidney injury, critical illness, renal replacement therapy, pharmacokinetics, population-based incidence, mortality, health-related quality of life, fluid accumulation

1. INTRODUCTION

The first descriptions of renal failure treated with dialysis, or renal replacement therapy (RRT), date back to 1960.[218] The continuous RRT technique was subsequently introduced, in 1977, first performed via an arteriovenous circuit.[130] Later, safer and more efficient venovenous techniques became the standard of care. During the last decades, these techniques have greatly improved and knowledge regarding the optimal practice of RRT has increased. Meanwhile, the concept of acute renal failure has evolved to encompass a syndrome, acute kidney injury (AKI), defined by a sudden decrease in the glomerular filtration rate (GFR).[160] Until recently, however, over 35 different definitions for AKI have complicated the diagnostics, patient care, and research.[123] The publication of Risk, Injury, Failure, End-Stage, Loss-of-function (RIFLE) criteria[19] and Acute Kidney Injury Network (AKIN) criteria[160] has facilitated research in this field. Kidney Diseases: Improving the Global Outcomes (KDIGO) – foundation recently published an update to these criteria.[120] Severe AKI treated with RRT is associated with severe sepsis in about half of the patients.[231] Other common underlying conditions include major surgery, hypovolemia, hypoperfusion, and exposure to nephrotoxic agents.[231]

The population-based incidence of RRT for AKI has varied from 4 to 96 per 100 000 adults per year[36,242] with a rising trend.[242] The incidence rate is broadly comparable to the incidence of acute respiratory distress syndrome.[209] The population-based incidence of RRT for AKI in Finland is unknown. Among all intensive care unit (ICU) patients, 3 to 8% have been reported to receive RRT for AKI.[55,231,196] Patients treated with RRT for AKI have high short-term mortality, up to over 60%,[230] which is among the highest of all patient groups treated in the ICU. Previous assessments regarding the mortality rates of these patients in Finland have been single-center studies, however.[128,258] The health-related quality of life of RRT-treated patients has been found to be impaired compared to the general population after long-term follow up.[258] Thus, despite recent advances in RRT, the mortality rate remains strikingly high, and improvements in the care of these patients would be essential.

RRT among the critically ill is a complex treatment. The results of treatment of several other complex procedures, such as highly technical surgery[21] and percutaneous coronary interventions[96] have been found to be better in centers with a high case volume of these patients. Some reports have suggested a volume-outcome effect also among ICU patients with mechanical ventilation[116] and severe sepsis.[192] Regarding patients with RRT, no volume-outcome effect was found in a large cohort study, in which ICUs participated on a voluntary basis.[174] Previously, among Finnish surgical patients with severe sepsis, hospital survival was found to be better in ICUs of large central hospitals or university hospitals compared to small central hospitals.[202]

The optimal time to initiate RRT is unclear. Two meta-analyses have concluded that early RRT initiation might be beneficial,[118, 219] however, the definition of "early" remains obscure. The only, small, randomized controlled trial investigating the timing of RRT did not find early RRT to be beneficial.[26] Among critically ill children, a clear

association of the presence of a high degree of fluid accumulation at RRT initiation with adverse outcome has been reported.[89,227] In critically ill adults, some studies have shown an association between higher degree of fluid accumulation 24h prior to RRT initiation[16] and three days preceding a nephrologist consultation[25] with increased risk for mortality. More evidence is urgently needed, but optimizing the timing of RRT initiation in relation to fluid accumulation, or using a more restrictive fluid management strategy could be potential means to improve the care of these patients.

As continuous RRT is the predominantly used RRT modality, and half of the patients suffer from sepsis,[231] adequate dosing of antimicrobial drugs is important. Among patients with CRRT, empirical dosing strategies have been found to lead to insufficient antibiotic concentrations.[207] The reporting of pharmacokinetic studies in CRRT-receiving patients has been found to be inadequate,[141] and individualized drug dosing is recommended.[44] The adequacy of the delivered CRRT dose used in the pharmacokinetic studies has not been evaluated, however. Evidently, ensuring the right dosing of antimicrobials in this complex patient group would be another way to provide better treatment.

The aim of this study was to evaluate the population-based incidence of RRT for AKI in Finland and the outcomes of these critically ill patients with RRT in two nationwide cohorts. Furthermore, the potential existence of a volume-outcome effect and the association of fluid overload at RRT initiation with outcome were investigated. Additionally, the quality of published pharmacokinetic reports in CRRT-receiving patients and the adequacy of the CRRT dose were evaluated.

2. REVIEW OF THE LITERATURE

2.1 DEFINITIONS

2.1.1 KIDNEY FUNCTION

Glomerular filtration rate (GFR) is the best measure of filtering capacity of the kidneys,[121] and thus kidney function. GFR describes the amount of plasma-like fluid filtered through the glomerular capillaries into the renal tubules in a unit of time.

$$\text{GFR (mL/min)} = \frac{Cu \times Qu}{Cp}$$

Cu = concentration of a substance mg/mL in urine
Cp= concentration of a substance mg/mL in (arterial) plasma
Qu=urine flow rate (mL/min)

Substances that are freely filtered through glomeruli and neither secreted nor reabsorbed can be used to measure GFR. The renal clearance of such substances equals GFR.[194] The gold standard of measuring GFR is inulin clearance,[194] but various isotopes[195] and iohexol[31] are also reliable. In clinical practice, the use of exogenous substances to measure GFR is impractical, and creatinine clearance (CrCl) is widely accepted as a surrogate marker for GFR.[119] Since creatinine is also excreted in the proximal tubule, use of CrCl is prone to bias.[194] Creatinine excretion rate is proportional to the serum concentration of creatinine, which causes overestimation of GFR.[194] Serum and plasma concentrations of creatinine have been shown to correspond.[158] Serum creatinine is related to age, gender, muscle mass, nutritional status,[138] and fluid status.[194]

CrCl can be measured by collecting daily urine and determining the plasma and urine creatinine concentrations.[63] Several equations have been developed to estimate CrCl or GFR from serum creatinine and other factors, the Cockcroft-Gault equation[53] being the oldest. The "Modification of Diet in Renal Disease" (MDRD) formula[137] can be used to estimate GFR normalized to body surface area in adults. From the original MDRD equation, an abbreviated equation without serum albumin and blood urea nitrogen values is usually used.[121] The most recently developed CKD-EPI equation accounts for age, gender and race.[139]

Cockroft-Gault equation:[53]

$$\text{CrCl (mL/min)} = \frac{(140-\text{Age}) \times \text{Weight}}{72 \times \text{SCr}} \times (0.85 \text{ if female})$$

MDRD equation (abbreviated "four variable equation"):[121]

GFR (mL/min/1.73m^2) = 186 x SCr $^{(-1.154)}$ x Age$^{(-0.203)}$ x (0.742 if female) x (1.212 if Afro-American)

CKD-EPI equation:[139]

GFR (mL/min/1.73m^2) = 141 x min(SCr/κ, 1)$^{\alpha}$ x max(SCr/κ, 1)$^{-1.209}$ x 0.993^{Age} x (1.018 if female) x (1.159 if Afro-American)

SCr= serum creatinine (mg/dL)

κ = 0.7 if female
κ = 0.9 if male
α = -0.329 if female
α = -0.411 if male
min = the minimum of SCr/κ or 1
max = the maximum of SCr/κ or 1

The accuracy of Cockcroft-Gault and MDRD equations to estimate GFR within a 30% range of the measured GFR has been evaluated.[121] The Cockcroft-Gault equation was found to fulfill this limit in a median of 75% of measurements, while over 90% of measurements were found to be within the range when the MDRD equation was used.[121] The CKD-EPI equation performed better in estimating GFR than the MDRD equation especially at higher GFR values in its validation study.[139] A systematic review confirmed this result, however it also found that the MDRD equation performed better in estimating lower GFR levels (<60 mL/min/1.73m^2).[70] The Acute Dialysis Quality Initiative[19] recommends the use of the MDRD equation.

Normal GFR ranges from 90 to 130 mL/min/1.73m^2, mildly decreased from 60 to 89, moderately decreased from 30 to 59, severely decreased from 15 to 29 and end-stage renal disease <15.[121] In clinical practice, a sudden decrease in urine output also serves as a surrogate marker for decreased GFR.[119]

2.1.2 ACUTE KIDNEY INJURY

Acute kidney injury (AKI) refers to a syndrome defined by an abrupt decrease in kidney function.[160] AKI encompasses a range of patients, from those experiencing only a minor decrease in GFR to those requiring renal replacement therapy (RRT). AKI patients demonstrate an increased mortality compared to patients without AKI.[39,105]

An acute deterioration of kidney function has been defined in more than 35 different ways in the literature,[123] which has complicated diagnostics, treatment, and research. The Acute Dialysis Quality Initiative published the Risk, Injury, Failure, Loss, End-stage disease (RIFLE) criteria based on changes in serum creatinine and urine output.[19] Later, the Acute Kidney Injury Network (AKIN) published the AKIN

classification with slight modifications to RIFLE, and proposed the definition of AKI to cover acute renal failure, acute tubular necrosis, and related diagnoses.[160] Both classifications have been validated in over 500 000 patients.[120] When the RIFLE and AKIN classifications were compared in the same cohort, RIFLE failed to find patients with AKIN stage 1 AKI, whereas AKIN did not identify patients with RIFLE risk or failure AKI.[111] Patients defined as having AKI using either of the classifications had increased mortality compared to patients without AKI.[111] The disparity between the classifications further advocated the development of a new AKI definition combining the two previous classifications.[120] All three classifications are presented in Table 1.

Table 1. Diagnosis and classification of AKI by RIFLE,[19] AKIN,[160] and KDIGO.[120]

RIFLE		**RIFLE and AKIN**	**AKIN**		**KDIGO**		
Class	SCr or GFR	Urine output	Stage	SCr	Stage	SCr	Urine output
Risk	Increased SCr x 1.5 or GFR decrease >25%	<0.5mL/ kg/h for ≥ 6 hours	1	Increased ≥26.5 or 1.5-2 –fold increase from baseline	1	1.5-1.9 times baseline or ≥26.5 increase	<0.5mL /kg/h for 6-12 hours
Injury	Increased SCr x2 or GFR decrease >50%	<0.5mL/ kg/h for ≥ 12 hours	2	Increased > 2-3 –fold from baseline	2	2.0-2.9 times baseline	<0.5mL /kg/h for ≥ 12 hours
Failure	Increased SCr x3 or GFR decrease >75% or SCr >354 with an acute rise of > 44	<0.3mL/ kg/h for 24 hours or anuria for 12 hours	3	Increased >3 –fold from baseline or SCr≥ 354 with an acute rise ≥44 or RRT	3	3.0 times baseline or SCr≥ 354 or initiation of RRT	<0.3mL /kg/h for ≥24 hours or anuria for ≥12 hours
Loss	Persistent acute renal failure = complete loss of kidney function >4 weeks						
End-stage	End-stage renal disease (>3 months)						

AKIN; Acute Kidney Injury Network; KDIGO; Kidney Disease: Improving Global Outcome; RIFLE; Risk, Injury, Failure, Loss, End-stage; RRT; renal replacement therapy; SCr; serum creatinine in μmol/L.
The class/stage is based on worst of either SCr or urine output criteria. Urine output criteria are identical for RIFLE and AKIN.
RIFLE: AKI should be abrupt (within 1-7 days) and sustained (over 24 hours).
AKIN: Increase in SCr must occur <48 hours.
KDIGO: Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within prior 7 days, increase in SCr ≥26.5 μmol/L within 48 hours.

2.2 EVALUATION AND TREATMENT OF ACUTE KIDNEY INJURY

The causes for AKI are traditionally classified into prerenal, intrinsic renal, and postrenal. Prerenal causes include factors leading to renal hypoperfusion and decreased GFR in an otherwise intact kidney, such as systemic hypotension and hypovolemia in septic shock. Intrinsic causes refer to processes affecting the structures of the kidney. Toxins (e.g. radio contrast agents, aminoglycosides, or peptidoglycan antibiotics) or ischemia may cause acute tubular necrosis. Other intrinsic causes include acute glomerulonephritis, acute interstitial nephritis, or vascular causes such as vasculitis. Postrenal causes refer to obstruction on the level of the collecting system, or bladder and ureters.[135] The most common underlying conditions of AKI are septic shock, cardiogenic shock, hypovolemia, and major surgery.[231]

In brief, the initial evaluation of AKI should include assessment of potential underlying causes for AKI and aiming therapeutic measures to prevent the worsening of or reversing the abnormalities.[100] The core of treatment of AKI according to expert panels[28,120] consists of avoiding nephrotoxic drugs, optimizing hemodynamics and volume status, preventing further injury, and in severe cases, RRT. In clinical practice, furosemide is often tried after volume resuscitation, however, it is only recommended for managing volume overload.[120]

The search for pharmacological interventions to prevent or treat AKI has been vigorous but results remain disappointing.[100] Low-dose dopamine, fenoldopam, or atrial natriuretic peptide are not recommended to prevent or treat AKI.[120] Furosemide is also not beneficial in the prevention of AKI.[101] The most recent promising results come from septic AKI patients treated with alkaline phosphatase.[199] The most common etiological factors are thought to lead to decreased renal blood flow, however, as the treatment strategies aiming at increasing the renal blood flow have failed, the approach may be wrong and even harmful.[38] Instead of increasing the work load of the injured kidney by fluid challenges and diuretics, a concept of "permissive hypofiltration" has been proposed.[38] The strategy is analogous to the treatment of acute respiratory distress syndrome and acute myocardial infarction, where an essential part of the treatment is to allow the injured organ to rest.[38] To rest the kidney, RRT should be provided early.[38]

2.3 INCIDENCE OF RENAL REPLACEMENT THERAPY FOR ACUTE KIDNEY INJURY

The annual population-based incidence of AKI defined by RIFLE has been reported to vary from 181 to 290 per 100 000 per year[2,36] and the population-based incidence for RRT for AKI from 4 to 96 per 100 000 per year (Table 2). The highest incidence has been reported in the United States from a community with an unrestricted access to intensive care, where the incidence of acute lung injury was also higher compared to other reports.[36] The population-based incidence of RRT for AKI is comparable to the

incidence of acute respiratory distress syndrome that has been reported to range from 13.5 to 58.7 per 100 000 per year.[149,209]

The incidence of RRT for AKI has been rising over the years; in a register-based study it rose from 4 per 100 000 in 1988 to 27 per 100 000 in 2002.[242] Several potential explanations for the rising trend in the incidence of RRT for AKI can be found. First, although no data of the population-based incidence of AKI of any severity over time exist, it is likely to have increased. In line with this, the proportion of ICU patients with AKI has been shown to increase over time.[11] Second, the availability of RRT has improved.

Of all ICU patients, 3.3% to 8.3% have been reported to receive RRT for AKI (Table 2). In the multinational Beginning and Ending Supportive Therapy for the Kidney (BEST) -study,[231] the proportion of patients in different countries with acute renal failure, of whom approximately two thirds received RRT, ranged from 2.1% to 22.1%. The large variation may imply nationally varying indications for RRT. Of RRT-treated AKI patients 14%[54] to 40% (excluding acute-on-chronic kidney disease)[200] have been reported to be treated outside ICUs. Of patients treated in the ICU, 45% to 98% have received CRRT (Table 2). The proportion of patients receiving RRT in the ICU is lower compared to the proportion of septic shock patients that ranges from 6.3% to 14.7%.[6]

Table 2. Studies reporting population-based incidence (per 100 000 per year) or proportion of ICU patients (%) of patients receiving RRT for AKI.

Reference	RRT patients	Time frame	Setting	Study type	RRT mo-dality[a]	Population -based incidence	Propor-tion of ICU patients
Waikar et al. 2006[242]	118 496	1/1988-12/2002	Registry	M, R	NA	4 - 27	NA
Korkeila et al. 2000[128]	62	1992-1993	ICU	S, R	CRRT IRRT	8	NA
Soubrier et al. 2006[224]	197	1/1995-12/2001	ICU	S, R	CRRT	NA	5.9
Cole et al. 2000[54]	135	9/1996-11/1996	ICU, ADU	M, P	CRRT (96%[a]) IRRT	13.4	NA
Hsu et al. 2007[106]	3885	1/1996-12/2003	Registry	M, R	NA	24.4	NA
Metnitz et al. 2002[165]	893	3/1998-2/2000	ICU	M, P	CRRT (90%) IRRT	NA	4.9
Bagshaw et al. 2005[12]	240	5/1999-4/2002	ICU	M, R	CRRT IRRT	11.0	4.2
Silvester et al. 2001[221]	299	3 months	ICU	M, P	CRRT (98%) IRRT	8	NA
Metcalfe et al. 2002[164]	48	5/2000-7/2000	ICU	M, P	NA	20.3	NA
Hoste et al. 2006[105]	219	6/2000-7/2001	ICU	M, R	NA	NA	4.1
Uchino et al. 2005[231]	1260	9/2000 - 12/2001	ICU	M, P	CRRT (80%) IRRT	NA	4.2
Prescott et al. 2007[200]	809	36 weeks in 2002	ICU, ADU	M, P	CRRT IRRT	28.6	NA
Cruz et al. 2007[55]	71	4/2003-6/2003	ICU	M, P	CRRT (98%) IRRT	NA	3.3
Yasuda et al. 2010[253]	242	1/2006-10/2006	NA	M, P	CRRT (74%) IRRT	13.3	NA
Cartin-Ceba et al. 2011[36]	97[b]	1/2006-12/2006	ICU	M, R	CRRT (45%) IRRT	96	5.7
Piccinni et al. 2011[196]	48	9/2009-4/2010	ICU	M, P	CRRT (96%) IRRT	NA	8.3

ADU; acute dialysis unit, CRRT; continuous renal replacement therapy, IRRT; intermittent renal replacement therapy, ICU; intensive care unit, M; multicenter, S; single center, P; prospective, R; retrospective, NA; not available
[a] of patients treated in ICU [b] calculated from percentage

2.4 RENAL REPLACEMENT THERAPY

2.4.1 INDICATIONS

Absolute indications

Generally accepted absolute indications for initiating RRT in AKI patients are 1) severe acidosis (pH <7.15), 2), 2) hyperkalemia (K>6.0 mmol/L and/or ECG abnormalities), and 3) fluid overload (pulmonary edema).[10,85, 120, 180] In addition, uremic complications (urea >36 mmol/L or pericarditis, pleuritis, bleeding, encephalopathy), urine output <200 mL/12h or anuria, and hypermagnesemia in the absence of deep tendon reflexes have also been listed as absolute indications for RRT.[10] Generally, before considering RRT initiation for these indications, the patient has also proven unresponsive to other treatment (eg. bicarbonate in acidosis or diuretics in fluid overload).[10, 120]

The proportion of patients fulfilling these absolute indications varies. In a prospective cohort study, 10.7% of patients had severe acidosis, 8.1% hyperkalemia, 30% fluid overload (>10% of body weight), and 21.4% had urea >36 mmol/L on RRT initiation, which occurred a median (interquartile range) of 1 (0-4) day(s) from ICU admission.[16] Oliguria was present in 33% and anuria in 20% of patients.[16] In the RENAL study, the reasons for randomization were as follows: severe acidosis (pH<7.2) in 35%, hyperkalemia (K>6.5 mmol/L) in 6-9%, severe edema associated with AKI in 43-45%, oliguria (urine output <400 mL/day) in 60%, urea >25 mmol/L in 39-44%, and creatinine >300 µmol/L in 39-48% of patients.[204] Mean (+-SD) time from ICU admission to randomization was 2 (4-5) days.[204]

Relative indications

In the absence of absolute indications for RRT in AKI, no consensus for RRT initiation exists. As in patients with chronic kidney disease, a tendency to avoid RRT as long as possible seems to be the current practice.[120] This is reasoned for the costs and potential harm of RRT, the potential recovery of the patient without RRT, and lack of scientific proof.[120] It is recommended to consider the overall clinical situation and severity of illness, presence of conditions that potentially respond to RRT, the success of other treatments in treating these conditions, and trends in the severity of AKI and laboratory values rather than single threshold values.[10,120, 110,180] Algorithms to aid clinical decision-making have been developed for AKI patients only,[180] and also to cover non-renal indications.[10] RRT initiation should be considered if AKI or general illness severity is rapidly worsening (sustained oliguria and progressive acidosis), in the presence of refractory fluid accumulation (and worsening pulmonary edema), severe sepsis, hypercatabolic state, permissive hypercapnia, and if renal reserves are reduced or early renal recovery seems unlikely.[10,180] The importance of regular re-evaluation of kidney function and the need for RRT is emphasized if an initial decision not to start RRT is made.[10,180]

Optimal patient selection for RRT is complex. Patients with RIFLE-Failure AKI not receiving RRT were found to have lower severity scores and more frequent treatment restrictions compared to RIFLE-Failure patients with RRT.[217] Those without treatment

restrictions displayed a lower mortality compared to patients treated with RRT, and died of non-renal reasons, implying that RRT would not have changed their course of illness.[217]

Non-renal indications

In the absence of AKI, indications for RRT include 1) severe fluid overload to remove fluid when diuretic therapy is not efficient enough 2) immunomodulation in septic shock 3) removal of endogenous (eg. myoglobin) or ingested toxins 4) management of severe dysthermia or electrolytic disturbances.[10] Lithium, ethylene glycol, and salicylates were the most common ingested toxins removed with hemodialysis in the United States.[103]

2.4.2 BASIC PRINCIPLES AND TREATMENT MODALITIES

Solute clearance in dialysis is based on diffusion. Diffusion is movement of solutes through a semi-permeable membrane in the direction of lower concentration until the solute concentrations are equal on both sides of the membrane. The proportion of solute concentration in the dialysate and in plasma is referred to as the saturation coefficient.[50] Generally small molecules are cleared by diffusion, however, the size of the molecules that can be cleared by diffusion depends on the pore size of the semi-permeable membrane. In hemofiltration, solute clearance occurs via convection (or solvent-drag), which is the movement of solutes along with the solvent across a semi-permeable membrane driven by a hydrostatic pressure gradient. Larger molecules, up to low-molecular weight proteins, are cleared by convection rather than by diffusion, however, the clearance depends largely on the pore-size of the membrane.[140] The sieving coefficient is the proportion of solute concentration transported through the membrane and concentration in plasma.[50]

Dialysis and other forms of RRT are performed in a closed circuit via a double-lumen catheter inserted in a central vein (or in ESRD patients, arteriovenous fistula), where venous blood is pumped via the so-called arterial line into the dialyzer. The dialyzer, or filter in convective modalities, consists of hollow fibers mimicking the capillaries of the kidney. Blood is circulated in the fibers that are separated by a semi-permeable membrane from the outer space, where the dialysis fluid is pumped in a counter-current direction. After blood is pumped through the dialyzer, it is returned to the patient via the venous line of the catheter. In hemofiltration, there is no dialysis fluid, but the plasma water and solutes are filtered through a semipermeable membrane, and replacement fluid is administered either pre-filter or post-filter to replace the filtered plasma water.

Intermittent hemodialysis (IHD) is the principally used intermittent RRT (IRRT) modality. IHD sessions typically last from 1.5 to 6 hours. Other IRRT modalities are intermittent hemodiafiltration, ultrafiltration, hemofiltration, and hemoperfusion. Special techniques for non-renal indications include plasmapheresis, light-chain dialysis, and molecular absorbent recirculating system (MARS) for acute liver failure.

Slow continuous ultrafiltration and sustained low-efficiency dialysis are so-called hybrid techniques between intermittent and continuous modalities.

Continuous RRT (CRRT) has been performed via a venovenous circuit, as described above, since the 1990s. CRRT is intended to run continuously throughout the day, providing better hemodynamic stability, and slower shifts in fluid and electrolyte balance.[124] Modalities include continuous venovenous hemofiltration (CVVH) (Figure 1a), continuous venovenous hemodialysis (CVVHD) (Figure 1b), and continuous venovenous hemodiafiltration (CVVHDF) (Figure 1c), where convective and diffusive clearances are combined. Bicarbonate-buffered dialysis and replacement fluids are recommended over lactate-buffered.[120]

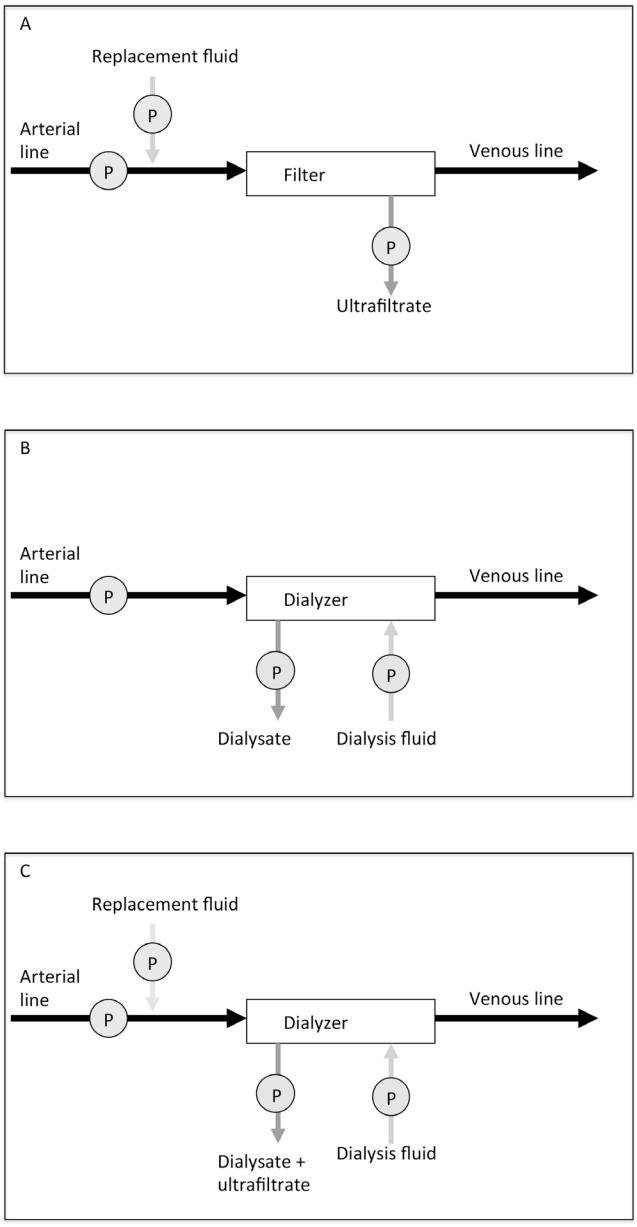

Figure 1. Schematic presentation of circuits of a) continuous venovenous hemofiltration with predilution b) continuous venovenous hemodialysis c) continuous venovenous hemodiafiltration with predilution. (P; pump)

2.4.3 ANTICOAGULATION

In the extracorporeal circuit, blood is in contact with foreign material activating coagulation pathways. To prevent blood clotting in the filter and to enable the delivery of treatment, anticoagulation is usually needed both in IRRT and CRRT. However, in the combination of critical illness, AKI, and possible bleeding risk -increasing conditions, such as recent major surgery or trauma, disseminated intravascular coagulopathy, or uremic complications of AKI, pros and cons of anticoagulation need to be considered individually. No thresholds for blood values to guide the decision have been established.[120]

In IRRT, in patients without coagulation abnormalities, unfractionated heparin or low-molecular-weight heparins (LMWH) are recommended.[120] Unfractionated heparin and LMWHs have been found to be equally safe and efficient in patients with chronic RRT.[142] In Europe, however, LMWHs are preferred due to easier administration and lower risk for heparin-induced thrombocytopenia observed in chronic RRT.[74] If coagulation abnormalities are present, IRRT is recommend to be performed without anticoagulation.[120]

In CRRT, the need for anticoagulation is continuous, and the patient is more prone to complications from anticoagulants. Regional anticoagulation of the extracorporeal circuit with sodium citrate has recently been introduced.[162] Regional citrate anticoagulation has been shown to reduce the risk of bleeding compared to unfractionated heparin[20,134,167] and to LMWH (nadroparin)[181] in RCTs. The use of citrate has also been associated with increased filter life span[134,167] and even with increased survival and renal recovery.[181] Thus, in the absence of contraindications for citrate, it is suggested as the primary anticoagulation method in CRRT in centers with established protocols for its use.[120] In the presence of contraindications, unfractionated heparin or LMWH are then recommended.[120] Citrate can, however, also be used in patients with increased risk for bleeding.[120]

Mehta et al.[162] first described regional citrate anticoagulation. Briefly, citrate is infused in the pre-filter arm of the circuit, where it binds calcium in the patient's blood thus inactivating coagulation. The citrate-calcium complex is partly dialyzed or filtered, and the remaining citrate returning to the patient is normally rapidly metabolized in the muscles or liver into bicarbonate, and the bound calcium is returned to circulation. Calcium is also substituted by a post-filter infusion.

In severe liver failure, citrate metabolism in the liver can be decreased.[129] Aerobic conditions in muscles needed to metabolize citrate can be also be compromised in severe shock.[182] In both of these conditions, citrate accumulation leading to hypocalcemia and metabolic acidosis can potentially occur.[182] In studies regarding regional citrate anticoagulation, patients with liver-failure have usually been excluded,[251] although recently citrate was found to be safe in liver-transplant recipients requiring CRRT in a retrospective study.[210] Metabolic alkalosis is another possible complication of regional citrate anticoagulation,[162] but in a meta-analysis comparing citrate to heparin, no significant difference in its occurrence was detected.[251] Consequently, using regional citrate anticoagulation requires a strict protocol and regular follow-up of the plasma ionized and total calcium levels.[182]

2.4.4 DOSE

Generally, in medical practice, targets of a therapy should be defined and measurable. Quantification of RRT dose in maintenance dialysis in ESRD patients is based on urea kinetics as urea serves as a surrogate marker for other low-molecular weight toxins: urea Kt/V describes the total treatment clearance of urea as a fraction of body water, where K is the dialyzer urea clearance, t the treatment time, and V the urea distribution volume.[91] Urea Kt/V is well validated in ESRD patients,[170] but the model is based on assumptions of a urea steady state in plasma and a normal urea distribution volume that are not met in critically ill AKI patients.[49,107] While no superior ways to quantify the IRRT dose in AKI patients exist, dose quantification using urea Kt/V is recommended.[120]

The quantification of CRRT dose is based on urea kinetics as well. Solute clearance is the ratio of solute concentration in the dialysate/filtrate and in plasma.[32] Free passage of urea through the dialyzer/filter with a sieving/saturation coefficient of 1 can be assumed.[32] Thus, the effluent flow rate normalized to patient body weight can be used as a surrogate for urea clearance.[208] The effluent flow rate in CVVH is the replacement fluid flow rate, in CVVHD is the dialysis fluid flow rate, and in CVVHDF is the sum of replacement and dialysis fluid flow rates. In convective modalities with predilution, the efficacy is reduced by about 15%, since the plasma entering the filter is already diluted.[32]

The dilution factor (Fd) can be calculated as follows:[50]

$$Fd = Qbw / (Qbw + Qr)$$

Qbw = blood water flow mL/h
(calculated from the blood flow rate multiplied by 1 -hematocrit)
Qr = replacement fluid flow in mL/h

Although effluent flow rate normalized to patient weight (mL/kg/h) is only a surrogate for the true dose, it is currently recommended for quantifying the CRRT dose, considering also the treatment time (hours of day).[120] Recently, urea and creatinine clearance during CVVHDF were measured in patients with a standard of dose 20 mL/kg/h and a high dose of 35 mL/kg/h.[150] Estimated urea clearance from the amount of spent effluent, also considering predilution and treatment time, was 15.8 mL/kg/h for the standard-dose group and 25.1 mL/kg/h for the high-dose group. The measured, true clearance in the standard-dose group was 15.6 mL/kg/h and in the high-dose group only 23.3 mL/kg/h, 35% less than prescribed. True creatinine clearance corresponded urea clearance in the standard group, but in the high dose group it was only 62% of the prescribed dose. Another study reported corresponding results; the true urea clearance was 22.3 mL/kg/h for a prescribed dose of 30 mL/kg/h.[51] The difference between estimated and true clearance of middle-sized molecules is likely to be even larger.[51] Filter clotting occurring over time is a potential explanation for the gap between the true measured dose and the estimated dose.[51,150]

2.4.5 DRUG PHARMACOKINETICS DURING RENAL REPLACEMENT THERAPY

Critical illness induces changes in drug pharmacokinetics. The volume of distribution (Vd) can be markedly increased due to volume load, leaky capillaries, and hypoalbuminemia causing decreased protein binding.[223] The increased Vd can lead to reduced plasma concentrations of especially hydrophilic drugs.[223] Only the unbound fraction of a drug is suspected to be eliminated by the kidney or by RRT.[131] Hepatic or renal dysfunction can reduce the amount of a drug normally metabolized and eliminated via these pathways and cause shifts in the distribution between hepatic and renal clearance.[223] RRT primarily affects the pharmacokinetics of drugs that are normally cleared renally.[33] Drugs with a small Vd (<1.0 L/kg),[33] and that are not highly protein bound, are likely to be removed with CRRT.[48]

Drug clearance during CRRT is affected by the modality, dose, and filter/dialyzer pore size, area, and age.[48] In addition, the Gibbs-Donnan effect affects the drug clearance,[33] although its clinical relevance is unclear.[44] Because negatively charged proteins are retained on the blood-side of the membrane, cationic drugs are filtered slightly less than anionic.[33] Generally, CVVH and CVVHDF are more effective in removing especially larger-sized drugs than CVVHD.[33,48] Higher effluent flow rates resulted in increased clearance of piperacillin-tazobactam although large inter individual variations were present.[233] However, a substudy of a multinational study did not find significant differences in the concentrations of empirically administered antibiotics in patients receiving a CRRT dose 25 vs. 40 mL/kg/h.[207] Furthermore, the antibiotic concentrations were outside the targeted range 25% of the time.[207] Patient's residual renal function during CRRT, although hard to measure, can also affect drug clearance. Additionally, drug may also be adsorbed to the filter,[191] which exerts saturation over time and this is not taken into account in drug dosing guidelines.[33]

Several strategies for individualized drug dosing during CRRT in the critically ill have been published.[33,44,212] In brief, since the loading dose depends only on the Vd, adjusting it because of CRRT is not necessary.[212] The Vd can be increased due to critical illness, however, and previously published data can be used to calculate a suitable loading dose.[44] The maintenance dose of the drug depends on the total clearance and is the sum of non-CRRT clearance and the CRRT clearance.[44] The CRRT clearance can be calculated on the basis of the CRRT modality, dose, and from the previously published Sc/Sd values.[44] A more accurate way would be to calculate the individual Sc/Sd values for the patient by measuring the plasma and dialysate/filtrate concentrations.[44] The non-CRRT clearance can be obtained from previously published values, but other organ failures such as hepatic failure should be accounted for.[44] Especially regarding drugs with a narrow therapeutic margin, therapeutic drug monitoring is recommended.[33]

2.5 OUTCOME

2.5.1 MORTALITY

Short-term mortality

In evaluating the outcome of ICU-treated patients, using a fixed endpoint such as 30- or 90-day mortality has been recommended.[88] Short-term mortality refers to hospital mortality or death at 28 or 30 days from ICU admission, RRT initiation or in RCTs, randomization. Among critically ill patients with RRT, high and greatly varying short-term mortality rates from 28% to 80% have been reported.[1,12,26,35,43,45,57,59,67,72,76,128,151,152,165,169,177,179,184,187,204,211,213,221,229,230,241,243,258] The great variability may be due to varying patient populations, different inclusion criteria, varying disease severity, and differences in used RRT modalities, RRT timing, and dosing. The severity of illness measured with the APACHE III score in the study with the lowest mortality rate[26] was lower than that of the RENAL study, [204] for instance (79-88 vs. 103). The studies reporting the highest mortality rates from 76 to 80% have been conducted in Brazil and Saudi-Arabia.[1,151] In the BEST study,[230] including ICUs from 23 different countries, the hospital mortality of patients with CRRT was 63.8%, and great differences between countries existed.

Data on improvement of the treatment results of RRT patients are conflicting. In the United States, a register-based cohort study that also included patients treated outside the ICU, found the mortality of RRT-treated AKI patients to decrease over time from 41% in 1988 to 28% in 2002, despite increased disease severity.[242] Another study found the mortality of ICU patients with any severity of AKI to decrease over time between 1996 and 2005 also after adjusting for covariates.[11] In a meta-analysis,[254] pooling studies among AKI patients with and without RRT from 1954 to 2003, however, the mortality rate remained rather steadily around 50%.

60-day or 90-day mortality and long-term mortality

After hospital discharge, late mortality and morbidity continue to occur.[4] Studies reporting 60-day or 90-day mortality and long-term mortality are presented in Table 3. Regarding short-term mortality, 60/90-day and long-term mortality rates are greatly varying. A cohort study[47] including only patients with surgical sepsis reported the highest 60-day mortality of 85%. Mortality rates at one year have varied from 57%[258] to 76%;[35] patients in the study by Carl et al.[35] had sepsis and were more severely ill than patients in the study by Åhlström et al.[258] After one year, mortality has been reported to increase from 57-65%[213,258] to 70-75% at five years.[214,258] However, in a large cohort study among all general ICU patients, the mortality rate paralleled the rate of general population after two years from initial ICU admission.[175]

Short-term mortality of other ICU patient groups

In the general ICU population, hospital mortality has varied from 11% to 64% depending on illness severity and case-mix.[249] During the past decade, hospital mortality rates of patients with severe sepsis or septic shock have been reported to range from 29%[80] to 62%.[73] As in studies in patients with AKI, varying definitions, patient populations, and treatment regimens seem to cause great variations in the mortality rates. A systematic review studied mortality in acute lung injury and acute respiratory distress syndrome from 1994 to 2006 and found an overall short-term mortality of 43% with an decreasing trend.[255]

Table 3. Outcome of patients treated with RRT for AKI.

	No of pts	Study type	RRT type	Disease severity	Mortality rates							Renal recovery[a] % of survivors (timepoint of assessment)
					Hospital	28/30-day	60-day	90-day	6-month	1-year	5-year	
Korkeila 2000[128]	62	S, R	CRRT, IRRT	NA	45				55		64.5	82 (6 months)
Metcalfe 2002[164]	52	M, P	NA	NA				73.5				93 (90 days)
Morgera 2002[169]	979	S, R	CRRT	APA II 20.5-21.9	69						84.5	90 (5 years)
Bagshaw 2005[12]	240	M, R	CRRT, IRRT	APA II 33	60	51		60		64		71 (1 year)
Luckraz 2005[148]	91[b]	S, R	CRRT	NA		42				47	48	97.8 (long-term, timepoint not defined)
Åhlström 2005[258]	681[c]	S, R	CRRT, IRRT	APA II 18		41				57	69.7	NA
Schiffl 2006, 2008[213,214]	425	S, P	CRRT, IRRT	APA III 88	47					65	75	95 (5 years)
Vinsonneau 2006[241]	360	M, RCT	CRRT, IRRT	SAPS II 65		59.7	68	72				99.5 (hospital discharge)
Bell 2007[18]	2202	M, R	CRRT, IRRT	NA				50				90.6 (90 days)
Prescott 2007[200]	809	M, P	CRRT, IRRT	NA			48					62 (90 days)
Darmon 2007[57]	91	S, P	CRRT, IRRT	SAPS II 46	42.9			63.1				NA
VA/NIH Network 2008[187]	1124	M, RCT	CRRT, IRRT	APA II 26	49.6		51.5-53.6					75 (60 days)[185]
Lin 2009[143]	342[d]	M, P	CRRT, IRRT	APA II 10-14				60				84.5 (90 days)
RENAL Investigators 2009[204]	1508	M, RCT	CRRT	APA III 103	44.2-44.4	38.5-36.9		44.7				93.2-95.6 (90 days)
Delannoy 2009[59]	205	M, P	CRRT, IRRT	SAPS II 63		45		56	62			88 (6 months)
Saudan 2006[211]	206	S, RCT	CRRT	APA II 24-26		51		54			70[e]	75 (90 day)
Carl 2010[35]	130	S, R	CRRT, IRRT	APA II 24.5		58.1				76.4		NA
Chou 2011[47]	279	S, R	CRRT	APA II 23.9			84.9					NA

APA; Acute Physiology and Chronic Health Evaluation; CRRT; continuous renal replacement therapy, IRRT; intermittent renal replacement therapy M; multicenter, NA; not available, P; prospective, R; retrospective; S; single center, SAPS; Simplified Acute Physiology Score

[a] defined as independency of RRT [b] cardiac surgical [c] includes 534 ICU and 147 acute dialysis unit patients [d] surgical patients [e] 3-year mortality

2.5.2 RENAL RECOVERY

Acute Dialysis Quality Initiative has defined the renal outcome after AKI either as complete or partial renal recovery, or ESRD.[19] In that definition, complete recovery is defined as returning to patients' initial RIFLE-class or as GFR at hospital discharge > 60mL/min/1.73m^2. Partial recovery is defined as a persistent change from the initial RIFLE-class or a GFR <60mL/min/1.73m^2 at hospital discharge without a need for RRT. ESRD is defined as dependency on RRT after three months from the initial insult. However, the study by Wald et al.[245] showed that even though patients were discharged from hospital without a need for RRT, the incidence of developing a chronic need for RRT was 2.63 per 100 person years after a median follow-up of three years. For comparison, the incidence for chronic RRT was 0.91 per 100 person years for patients hospitalized for other reasons than AKI and not receiving RRT during the index hospital period.[245] Thus, although patients may initially recover their kidney function, AKI seems to be a risk factor for further development for ESRD.[244] To enhance the possibility of generalizing between different studies, assessing renal recovery at 90 days has been proposed.[153]

Renal recovery rates of RRT-treated patients are presented in Table 3. The renal recovery rate defined as independency of RRT and measured after 60 days to 5 years from initial insult has varied from 62 to 98% (Table 3). One study reported a renal recovery rate at hospital discharge as 99.5%.[241] The study by Prescott et al.[200] with lowest renal recovery rate (62%) also included patients with acute-on-chronic kidney disease, while 87% of survivors with de-novo AKI recovered. Patients with sepsis or post-surgical AKI recovered more often.[200] Studies with lower renal recovery rate seem to have also lower mortality rate, implying that part of the patients who died in other studies might not have recovered their renal function had they survived.[153,206] Neither RRT modality,[232,241] nor dose[204, 187] have been shown to affect renal recovery in RCTs, although patients with CRRT had better renal recovery rate in a cohort study.[18] Regarding biomarkers, plasma NGAL was not found to be useful in predicting renal recovery,[56] however using a panel of urinary biomarkers might be useful.[225] Furosemide infusion after CRRT cessation improved urine output volume but did not affect renal recovery rate in a single-center RCT.[234]

2.5.3. HEALTH-RELATED QUALITY OF LIFE

Survivors of critical illness continue to suffer from long-term morbidity.[62] Health-related quality of life (HRQOL) after intensive care is an important measure of long-term outcome.[4] To measure HRQOL, the Short form -36 (SF-36)[246] or EuroQOL EQ-5D[75] instruments are recommended after at least six months of follow-up.[4] Both instruments include questions related to physical and mental health as well as a question for assessing the overall health status,[75,246] and answer given by patient's proxy have been found to be reliable.[102]

A systematic review of HRQOL studies concluded that survivors of critical illness have poorer HRQOL compared to the general population both at baseline (time preceding ICU admission) and after long-term follow up, although HRQOL improved over time after discharge.[65] Age and high disease severity were predictors of poorer HRQOL after follow-up.[65] Two thirds of survivors of critical illness have reported their own perception of health to be good at 90 days after admission.[34] Factors found to predict poor HRQOL were unplanned admission, hypothermia, metastatic cancer, pH below 7.25, and creatinine > 176 μmol/L on admission.[34] A meta-analysis among survivors of acute respiratory distress syndrome[64] and a systematic review including studies in sepsis patients[250] have shown that HRQOL remains impaired.

The HRQOL of patients who have received RRT during their ICU stay has been reported to be impaired measured either with the SF-36,[59,176] EQ-5D,[258] Health Utilities Index,[112] or the Nottingham Health Profile.[90, 128, 169] The HRQOL has been compared to either previous normative values obtained from general population[59,112,128,176] or the values of age and gender matched general population.[258] Problems in physical health have been described in particular.[59,258] In the study by Johansen et al.,[112] a quarter of the patients reported an extremely low HRQOL score at 60 days. In another report from the same cohort, HRQOL was found to be a predictor of mortality at one year.[113] Intensity of RRT or RRT dependency did not affect HRQOL, but longer hospital stay was associated with worse HRQOL.[112] In contrast to these findings, Gopal et al.[90] and Delanney et al.[59] have reported that a majority of patients would undergo the same treatment again if necessary and perceived their health state as acceptable or good.

2.6 PATIENT-RELATED FACTORS AND MORTALITY IN RRT PATIENTS

2.6.1 ADMISSION TYPE

The ICU admission type (medical, scheduled surgical, unscheduled surgical) is included in several ICU outcome-predicting models. Unscheduled surgical admission is associated with the highest risk for hospital mortality in the SAPS II model.[136] RRT patients with surgical admission have been found to have an increased risk for long-term mortality.[200,214] In the multicenter BEST study the admission diagnosis "respiratory surgery" was strongly associated with an increased risk for hospital mortality, although surgery as a contributing factor to AKI decreased the risk.[230] In a study that also included AKI patients without RRT, both admission for non-cardiac surgery and cardiac surgery compared to medical admission were found to reduce the risk for one-year mortality,[13] although these patients were probably at least partly elective and thus had better prognosis. Need for RRT after cardiac surgery has been found to independently increase the mortality among cardiac-surgery patients.[41] Thus, if surgery is the cause of AKI, the patient may have better prognosis than patients with other reasons for AKI, but (non-elective) surgical admission is probably not associated with better survival.

2.6.2 SEVERITY OF DISEASE, AGE, AND CO-MORBIDITIES

Higher disease severity measured either by APACHE II,[12,98,211] SAPS III on the first ICU treatment day, [152] or SOFA score on the day of RRT initiation[133,143] has been shown to be associated with higher mortality. However, of the general disease severity scores (APACHE II, SAPS II, and Mortality Probability Model at 24h II), none has proved to be confident enough for predicting individual patients' outcome.[77] Recently, a model for predicting 60-day mortality of RRT-receiving patients was developed, however, it has not yet been validated in other populations.[60] Also, the number of non-renal organ failures,[17,40,151] or separately liver failure,[12,35,179] respiratory failure or the need for mechanical ventilation,[179,230] need for vasoactives,[41,46, 179] hematological failure,[35,179] or neurological failure[179] have been associated with increased risk for mortality. Not surprisingly, increasing age,[59,143,151,230] presence of co-morbidities,[59,151] and worse functional status[151] have been associated with worse outcome. A strong association of age and comorbidities with mortality has also been reported among patients with sepsis.[5] Increased body mass index has been shown to associate with increased AKI incidence, but if RRT was required, adjusted mortality rates were lower in patients with body mass index ranging from 25 to 35 compared to normal- or underweighted patients.[67]

2.6.3 SEPSIS

Sepsis has been found as an underlying cause of AKI in 43 to 70% of patients.[12,173,221,231] Patients with septic AKI have been reported to have higher disease severity and mortality compared to patients with non-septic AKI.[14,173] In the multinational BEST study,[14] septic AKI patients (of whom 71% received RRT) had a hospital mortality of 70% compared to non-septic AKI patients with a mortality of 52%. Septic patients had a longer delay before initiation of RRT (a median of two days vs. one day) compared to non-septic, and time from ICU admission to RRT initiation was also independently associated with increased mortality.[14] In the same study, septic AKI was an independent risk factor for mortality after adjusting for severity of illness, age, baseline kidney function, admission type, and country.[14] High 60-day mortality rates from 68% to 85% have been reported for patients with septic shock and RRT with an APACHE II score of 24-25.[35,47] The presence of sepsis or severe sepsis has also been associated with an adverse outcome in several other studies.[12, 42,143,200,224]

2.5.4 BIOMARKERS

Red blood cell distribution width

Red blood cell distribution width is a marker in normal blood count that describes the size variation of the circulating red blood cells. Processes related to increased red blood cell destruction and ineffective erythropoiesis cause variation in red blood cell distribution width.[81] It has been related to worse prognosis among patients with coronary artery disease and heart failure, possibly because of increased inflammation and malnutrition.[81] Red blood cell distribution width over the normal limit at RRT initiation was associated after adjustments with an increased risk for short-term mortality in patients with CRRT.[177]

Novel biomarkers

Plasma neutrophil-associated lipocalin (NGAL) is an early biomarker for AKI.[56] It has been shown to both detect AKI 48 hours prior to clinical diagnosis in the general ICU population and predict the need for RRT.[56] Moreover, plasma NGAL measured at the time of RRT initiation was reported to predict 28-day survival.[133] Urinary NGAL can differentiate between pre-renal AKI and intrinsic AKI in patients with established AKI already, and predict their adverse outcome (rise of RIFLE-class, need for RRT, or death).[222] In a meta-analysis, both plasma and urine NGAL were found to be good diagnostic markers and predictors both for RRT and outcome.[93]

Cystatin C measured in plasma can be used to diagnose and predict AKI,[256] but its performance in predicting the need for RRT or mortality does not seem to be superior to serum creatinine, blood urea nitrogen, or urine output.[193] Angiopoetin-2 facilitates endothelial activation and inflammation,[78] and measured at RRT initiation, it has been shown to be a good predictor of 28-day outcome in patients with RRT.[132] Osteopontin, a cytokine, has also been suggested as a novel biomarker for predicting outcome in patients with RRT.[146]

Micro-RNAs regulate gene expression and circulate in plasma in a stable form, which can be measured by quantitative real-time PCR.[166] Briefly, deregulation of selected micro-RNAs may be disease specific, and cause changes in gene expression ultimately leading to disease processes.[228] Plasma level of miR-210 was found to be upregulated in AKI patients with RRT compared to healthy controls or patients with myocardial infarction.[147] Elevated miR-210 levels were associated with 28-day mortality, however, with an AUC of only 0.7.[147]

To summarize, the vigorous search for novel biomarkers able to diagnose AKI before clinical diagnosis, stratify the severity of AKI, predict the need for RRT, and predict outcome is ongoing. Thus far, plasma NGAL seems most promising in predicting both the need for RRT and outcome,[56] however, none of the novel biomarkers is in routine clinical use.

2.7 RENAL REPLACEMENT THERAPY -RELATED FACTORS AND OUTCOME

2.7.1 TIMING

Consensus exists neither on the optimal timing of RRT initiation for AKI nor on which parameter is the most suitable to define "timing". Apart from immediate indications for RRT, the decision to initiate RRT is mainly based on clinical judgment. Recent meta-analyses[118, 219] and a systematic review[180] concluded that early RRT might be beneficial. One small RCT studied timing randomizing patients regarding time from ICU admission into early or late CRRT, and found no survival benefit for the early RRT.[26] Another small RCT studied RRT initiation as soon as urine output decreased to a level <30 mL/h (early) compared to <20 mL/h (late), and found over 6-fold lower mortality in the early RRT group.[226]

Bagshaw et al.[16] studied characteristics of patients at RRT initiation, and found that patients with multiple triggering factors for RRT had higher mortality compared to patients with few triggers. They also found that the longer time from ICU admission to RRT initiation associated with increased risk for mortality, as reported also previously.[178] The shorter ICU stay prior to randomization and RRT initiation in the RENAL study compared to another large RCT[187] (2 vs. 4 days) has also been suggested as one possible explanation for the lower mortality in the RENAL study.[186]

As in ESRD patients, implementation of thresholds of blood levels of creatinine, urea, or blood urea nitrogen (mg/dL can be converted to urea mmol/L multiplying by 0.357) has been studied in several observational cohort studies. Cut-offs for blood urea nitrogen between 60 mg/dL and 100 mg/dL to define early RRT have been studied, all studies finding better outcome for early RRT.[35,84,197,252] However, regarding time from ICU admission to RRT initiation in these studies, early has meant 4.4 to 10.5 days and late 11.3 to 19.4 days,[35,84,252] which compared to a recent practice study is not very early.[230] Bagshaw et al.[16] used a urea cut-off of 24 mmol/L and creatinine 309 μmol/L to define early and late, and found no difference in mortality. However, when patients were classified according to time from ICU admission to RRT initiation, patients with early (<2 days) RRT survived better.[16] Moreover, using relative changes of creatinine and urea values from ICU admission to RRT initiation, the change in urea was not associated with an increased risk for hospital death,[16] but results regarding serum creatinine values have been conflicting.[15,16] When serum urea was studied either as a continuous variable or as a categorical variable with different cut-offs, no association with hospital mortality was found.[58]

The suitability of RIFLE classification to define timing of RRT has been studied in two cohorts of surgical ICU patients using only the RIFLE-creatinine criteria.[47,220] Earlier RRT (RIFLE-Risk or no AKI) was found to associate with better outcome among gastrointestinal surgery patients.[220] This finding was not confirmed in a larger, and more heterogeneous surgical cohort concluding that RIFLE is a poor tool for classifying the timing of RRT.[47] Among general ICU patients with RRT, RIFLE class was not found to be associated with mortality.[151] Moreover, Bagshaw et al.[16] found no association of

RIFLE class (using both creatinine and urine output criteria) and mortality. Besides the fact that RIFLE has not been designed to predict the outcome of patients with RRT, the conflicting results of studies using only creatinine criteria might be explained by the fact that lower creatinine at RRT initiation indicates the presence of more urgent indications for RRT initiation than the accumulation of uremic toxins, e.g. acidosis or volume overload and the subsequent increased volume of creatinine distribution.[154,179] Moreover, higher creatinine at RRT initiation has been associated with better outcome,[15,37,179] possibly related to better nutritional status or underlying chronic kidney disease and, thus, different course of illness.[15]

Several retrospective studies in cardiac surgical ICUs have compared decreased urine output not responding to fluid and/or diuretic treatment as a trigger for early RRT initiation.[61,71 109,156] Compared to late initiation defined either as marked increase in creatinine[71, 61,156] or delaying RRT initiation 48h after diagnosing AKI,[109] patients with early RRT survived better. A strong association between decreased urine output and mortality has also been found.[16]

Fluid accumulation and edema are common indications for RRT.[16,204,230] Among patients with acute lung injury, a conservative fluid management strategy compared to a liberal strategy lead to better survival without increasing the need for RRT.[248] A further analysis of patients with AKI from the same study showed that after adjusting for multiple covariates, more positive fluid balance after AKI diagnosis was associated with mortality although crude mortality did not differ significantly.[92] Similarly, a small retrospective study in patients with septic shock found that patients achieving a negative balance during their first three days in the ICU survived better.[3] In fact, fluid balance as biomarker of critical illness has been proposed.[9] Several studies among critically ill children with CRRT have reported an association between a higher degree of fluid accumulation and worse outcome.[89,97,227] Non-survivors in a cohort study including AKI patients with and without RRT had a significantly more positive daily fluid balance compared to survivors.[189] An association between mean daily fluid balance after RRT initiation and mortality has also been found.[205] Among RRT patients, after adjusting for dialysis modality and APACHE III score, patients with fluid accumulation >10% of baseline weight at RRT initiation had an OR of 2.07 for death.[25] Another study found an association between degree of fluid accumulation from the 24h preceding RRT initiation and mortality.[16] Thus, initiating RRT before severe fluid accumulation may improve outcome.

2.7.2 MODALITY

Whether critically ill patients with AKI should receive intermittent or continuous RRT has been addressed in many RCTs. A French multicenter RCT found no difference in the 60-day survival or occurrence of hypotension in patients with acute renal failure (creatinine over 310 μmol/L or urea >36 mmol/L) and multiple organ dysfunction receiving CVVHDF compared to patients with IHD.[241] When post-dilution CVVH was compared to IHD in patients stratified according to the severity of illness, no difference in survival between the groups was found, although patients with coagulation

disturbances and severe hemodynamic instability were partly excluded.[145] When CVVHDF was also compared to IHD in a trial where significant differences in disease severity between the treatment groups existed, again, no difference was found after adjustments for disease severity.[161] Similar results have also been reported from single-center RCTs comparing CRRT and IHD[7,176,232] and CRRT compared to extended daily dialysis.[125] One RCT did report a significant decrease in mean arterial pressure in patients during IHD, which however, did not affect survival.[7] The hemodynamic tolerability of sustained low-efficiency dialysis has been found to be comparable to CRRT in an observational cohort study.[79] A meta-analysis[8] and a systematic review[188] found no differences in survival between CRRT and IHD patients. A Cochrane meta-analysis concluded that no modality was preferred over another in hemodynamically stable patients, but CRRT was associated with greater hemodynamic stability,[201] and, thus CRRT is suggested to be preferred among hemodynamically unstable patients.[120]

2.7.3 DOSE

The optimal RRT dose for critically ill AKI patients has been intensively researched during the last decade; however, only one study has focused on the optimal intensity of IHD comparing daily IHD sessions to alternate day IHD.[215] In this study, patients in the daily IHD group were found to have lower mortality and better control of uremia:[215] the urea Kt/V was 1.2 per IHD session.[215]

Ronco et al.[208] conducted the first RCT comparing different dosing strategies in CRRT. Patients were randomized to receive postdilution CVVH either 20 mL/kg/h, 35 mL/kg/h or 45 mL/kg/h. Patients receiving a dose of 20 mL/kg/h had significantly higher mortality compared to the two groups with a higher dose. No difference in mortality was found between the two groups with the higher dose, and a dose of at least 35 mL/kg/h was recommended. Several smaller RCTs have also compared CVVH or CVVHDF with a lower dose of 19-25 mL/kg/h to a more intensive dose ranging from 35 to 48 mL/kg/h.[26,211,229] Two of these studies[26,229] found no survival benefit of higher dose in terms of short-term survival, whereas patients with higher dose in the study by Saudan et al.[211] had a lower 90-day mortality rate compared to patients with a less-intensive dose.

A large multicenter RCT[187] (ATN study) with 1124 patients compared intensive RRT (IHD or sustained low-efficiency dialysis 6 times a week or CVVHDF 35 mL/kg/h) to less-intensive treatment (IHD or sustained low-efficiency dialysis 3 times a week or CVVHDF 20 mL/kg/h) in terms of 60-day survival. Kt/V for intermittent modalities was 1.3 per session. No difference in survival was detected between the intensive and less-intensive treatment. Notably, the median daily duration of CRRT was 21 hours for both groups, and 89% of prescribed CRRT dose in the intensive group, and 95% in the less-intensive group, was delivered.

In the RENAL study,[204] 1508 patients were randomized to receive either a lower dose of 25 mL/kg/h or a higher dose of 40 mL/kg/h of postdilution CVVHDF. No difference in the 90-day mortality between these two strategies was found, although the mortality rate was lower than in the ATN study[187] despite comparable disease

severity: 44.7% in RENAL vs. 51.5-53.7% in ATN. The delivered dose was 84% of the prescribed dose in the higher intensity group and 88% in the lower-intensity group.[204] The results of IVOIRE (high volume in intensive care) study[104] comparing CVVH 35 mL/kg/h to 70 mL/kg/h in septic patients have not yet been published completely, but the overall 90-day mortality was 51%.

Several meta-analyses regarding the intensity of RRT have concluded that higher intensity does not improve survival and a CRRT dose of 20-25 mL/kg/h is sufficient,[114,172,247] which is also the recommendation of KDIGO.[120] The delivered CRRT dose measured as spent effluent is clearly less than the prescribed dose.[187,236,237] Subsequently, to ensure that delivered dose reaches 20-25 mL/kg/h, prescription of a higher dose, approximately 30 mL/kg/h, has been recommended.[24,155,120] Moreover, setting individualized targets for fluid balance, electrolyte and acid-base homeostasis, and adjusting the RRT to achieve these targets is suggested.[120,238] The targeted dose should be prescribed, and the actual delivered dose assessed regularly,[120,155] which, however, is not the current practice.[183] Regarding IRRT, delivering a Kt/V of 3.9/week is recommended.[120]

2.7.4 CASE VOLUME

Association with high case volume and improved outcome has been documented in several fields of surgery,[21,95] as well as in percutaneous coronary interventions.[96,159] Depending on the type of the procedure, factors related both to the hospital's case volume and the operating physician's case volume play a role.[22,94] For example, in carotid endarterectomy, the case volume of the surgeon accounted for the volume effect more, but in lung cancer surgery that frequently involves complications, hospital facilities such as intensive care, pain management, and nursing care had a greater role.[22] Deaths could potentially be avoided if treatment of certain conditions, such as elective abdominal aneurysm repair or pancreatic and esophageal cancer surgery, would be concentrated to high-volume centers.[68]

Medical ICU patients with higher disease severity and gastrointestinal diagnoses had lower adjusted mortality rate in high-volume ICUs, whereas no volume-outcome association was observed among patients with respiratory or neurological diagnoses.[69] Among general ICU patients, no volume-outcome association was seen in the whole population, although an association with better outcome was noted in ICUs treating high volumes of high-risk patients after adjusting for patient risk factors and ICU characteristics.[87] Regarding ICU patients with severe sepsis,[192] with septic shock and malignancy,[257] and non-surgical patients needing mechanical ventilation,[116] treatment in high volume ICUs has been associated with better outcome. Potential explanations for the positive volume-outcome effect seen in these subgroups of ICU patients can include: better experience gained in treating high volumes of these patients, possibly better adopted treatment protocols in high volume ICUs, and organizational factors related to high ICUs such as multidisciplinary teams.[115] In contrast, among surgical patients[171] and general ICU patients[168] on mechanical ventilation, no volume outcome-effect could be demonstrated.

Only one previous study has investigated the volume-outcome effect in patients treated with RRT.[174] Nguyen et al.[174] studied 9 449 French and 3 498 U.S. non-surgical patients retrospectively during a ten-year period. The participating ICUs were divided into quartiles according to the annual case volume of RRT treated patients, which was one to nine patients in the smallest quartile in the U.S. cohort and 59 to 129 in the largest quartile in France. Notably, in the ICU quartiles, the proportion of patients treated with CRRT was only 14% to 56%, mainly under 30%. After adjusting for patient characteristics, hospital and ICU characteristics, no volume-outcome effect could be demonstrated. Thus, the potential effect of high volume on outcome among ICU patients remains inadequately answered.

3. AIMS OF THE STUDY

The main aims of this study were to evaluate the incidence of RRT for AKI in Finland and the outcome and factors associated with outcome in patients receiving RRT for AKI. Specific objectives were:

1. To systematically review the quality of published reports regarding drug pharmacokinetics during CRRT and evaluate the used CRRT dose in these studies (I)

2. To evaluate the population-based incidence of RRT treatment for AKI in Finland (II, IV)

3. To describe the RRT treatment given in Finnish ICUs (IV)

4. To investigate the short-term (II, IV) and long-term (II, IV) mortality of RRT patients treated in Finnish ICUs, and factors associated with mortality, specifically
    a. ICU size and annual case volume of RRT (III)
    b. Fluid overload at RRT initiation (IV)

4. MATERIALS AND METHODS

4.1 MATERIALS

A summary of the study characteristics is presented in Table 4. Study I was a systematic review including 49 original publications reporting drug pharmacokinetics during CRRT (Figure 2a). Studies II-IV included altogether 25 200 patients (Figure 2b). For studies II-III, data of all admissions in the 24 member ICUs of the Finnish Intensive Care Consortium during the study period from 1 January 2007 to 31 December 2008 were obtained. The 1558 patients in study III comprised a subcohort of study II. Study IV was a part of the FINNAKI study conducted in 17 ICUs between 1 September 2011 and 1 February 2012. Patient characteristics in studies II-IV are presented in Table 5.

The ethics committee of the Department of Surgery, Hospital District of Helsinki and Uusimaa waived the need for consent in studies II-III. In study IV, the study protocol and the use of deferred consent with a signed informed consent from the patient or proxy were approved. The Finnish National Institute of Health gave approval for the collection of data from medical records of deceased patients if consent could not be obtained.

Table 4. Study characteristics.

Study #	Study design	Patient #	Main objectives
I	Systematic review		Quality of pharmacokinetic studies and the adequacy of the used CRRT dose
II	Retrospective cohort	24 904	Incidence of RRT for AKI, mortality and HRQOL of RRT-treated patients
III	Retrospective cohort	1558	Association of ICU size and annual case volume with hospital mortality of RRT-treated patients
IV	Prospective observational cohort	296	90-day mortality and factors associated with it, especially fluid overload

AKI; acute kidney injury, CRRT; continuous renal replacement therapy, HRQOL; health-related quality of life; ICU; intensive care unit; RRT; renal replacement therapy

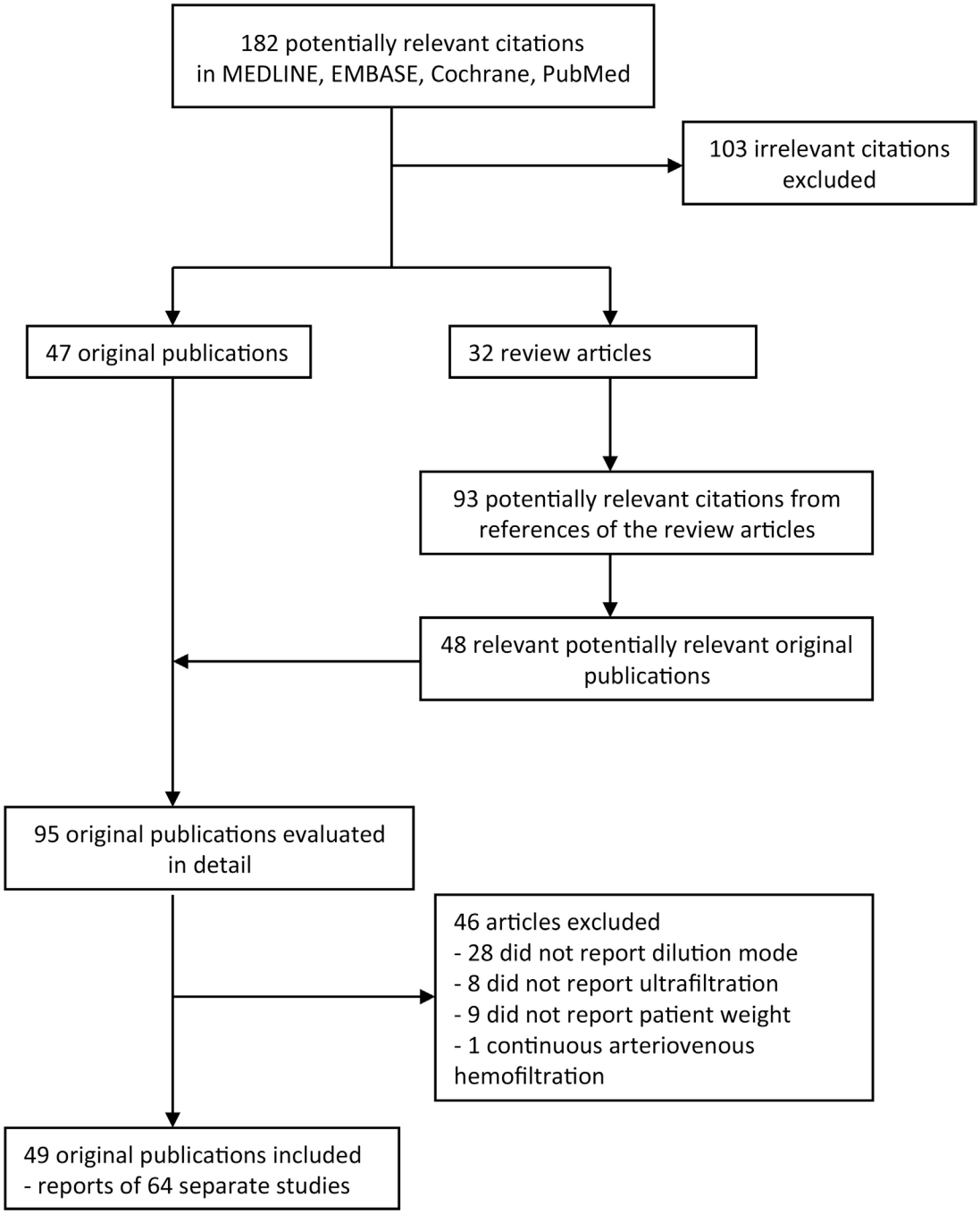

Figure 2a. Flow chart of study I.

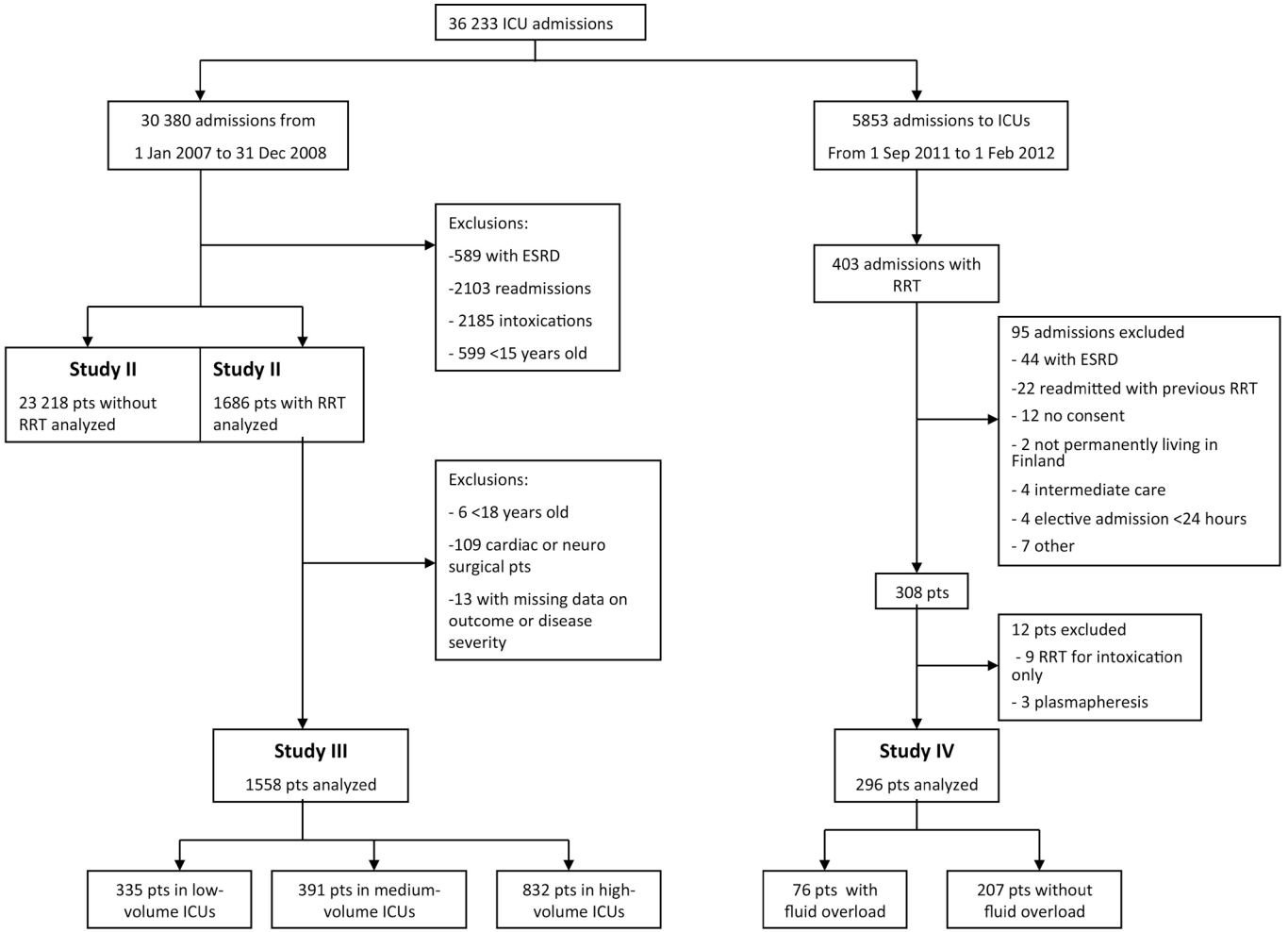

Figure 2b. Flow chart of studies II-IV.

Table 5. Patient characteristics.

	Study II		Study III	Study IV
	Non-RRT N=23218	RRT N=1686	RRT N=1558	RRT N=296
Age (years)	62 [50-73]	63 [52-72]	63 [52-72]	64 [55-73]
Male gender	14641/23200 (63.1%)	1143/1685 (67.8%)	1059/1557 (68.0%)	197/296 (66.6%)
Emergency admission	19122/23202 (82.4%)	1558/1684 (92.5%)	1499/1556 (96.3%)	271/292 (92.8%)
Surgical admission	9426/23208 (40.6%)	410/1685 (24.3%)	298/1557 (19.1%)	94/295 (31.9%)
SAPS II score	33 [23-46]	48 [37-62]	50 [39-63]	51 [40-65]
SOFA score (first ICU treatment day)	6 [3-8]	10 [7-13]	10 [7-13]	10 [8-13]
Mean daily TISS score	28.7 [22.4-35.0]	36.4 [29.7-43.2]	36.2 [29.6-43.0]	37.6 [32.3-44.2]
Mechanical ventilation[a]	11116/22409 (49.6%)	1014/1642 (61.8%)	938/1558 (60.2%)	189/290 (65.2%)
Vasoactives[a]	9556/23175 (41.2%)	1067/1671 (63.9%)	994/1558 (63.8%)	201/296 (67.9%)
ICU length of stay (days)	1.5 [0.9-3.2]	5.2 [1.9-10.8]	5.3 [1.9-10.8]	5.5 [2.2-10.9]
Hospital length of stay (days)	9 [5-16]	16 [8-29]	16 [8-29]	14.5 [6.0-27.3]

Continuous data expressed as median [IQR] and categorical data as number/total number (%).
ICU; intensive care unit; IQR; interquartile range, non-RRT; patients without renal replacement therapy, RRT; renal replacement therapy, SAPS; Simplified Acute Physiology Score, SOFA; Sequental Organ Failure Assessment, TISS; Therapeutic Intervention Scoring System
[a] On the first 24h of ICU treatment

4.2 STUDY DESIGNS

Study I

For this systematic review, a search was performed in Medline, PubMed, EMBASE, and Cochrane databases considering all citations entered in the databases by 31 December 2009. The search terms are presented in Table 6. Two independent reviewers screened all citations for relevance according to the inclusion criteria (Table 6). To supplement the database search, the bibliographies of the relevant review articles found in the search were also screened. Finally, 49 articles fulfilled the inclusion criteria (Figure 2a). These articles reported from 64 separate pharmacokinetic studies. The general quality of the included studies was assessed with the Downs and Black quality score index.[66] To evaluate the adequacy of reporting CRRT-related data, the Acute Dialysis Quality Initiative minimum reporting criteria for CRRT studies were used.[86,124] The mean CRRT dose used in the participating studies was calculated according to previous equations.[50]

Table 6. Literature search strategy and inclusion criteria for study I.

Search strategy
1. “acute kidney injury” OR “acute renal insufficiency”
2. “renal replacement therapy”
3. “pharmacokinetics”
4. “critical illness” OR “intensive care” OR “critical care”
Terms 1 to 4 were combined with Boolean operator AND
Inclusion criteria
1. reported original data from a primary publication reported in English
2. reported data from adult human subjects
3. included critically ill subjects receiving continuous venovenous RRT for AKI
4. focused on drug pharmacokinetics
5. reported parameters needed for calculation of continuous RRT dose

AKI; acute kidney injury, RRT; renal replacement therapy

Study II

In this retrospective cohort study, patients who received RRT for AKI were identified and compared to patients without RRT in terms of mortality and HRQOL. Altogether 30 380 admissions to Finnish Intensive Care Consortium member ICUs were screened. Readmissions, patients with end-stage renal disease, patients <15 years old, and patients who were admitted because of drug or alcohol intoxication were excluded (Figure 2b). For incidence calculations, data on the Finnish population over the age of 15 on 31 December 2007 were obtained from Statistics Finland.

Study III

In this retrospective cohort study, the crude and adjusted mortality of RRT-treated patients were compared in; 1) small vs. large ICUs and, 2) in low, medium, and high volume ICUs classified according to the annual case volume of RRT-treated patients. From the 2413 patients with RRT in study II, cardiac surgical and neurosurgical patients, patients without data on outcome or SAPS II or SOFA severity scores, and patients under 18 years of age were further excluded (Figure 2b).

Study IV

The FINNAKI study was a prospective, observational, cohort study. Factors associated with 90-day mortality of RRT-treated patients with special emphasis on fluid balance prior to RRT initiation were analyzed. During the five-month study period, the 5853 ICU admissions in the participating ICUs were screened for eligibility. All emergency admissions and elective admissions with an expected stay over 24h were included in the FINNAKI study. Patients who received RRT for AKI were included in study IV. The following patient groups were excluded; 1) patients with ESRD on maintenance dialysis, 2) patients who had already participated in the study and who had received RRT already on that previous admission, 3) patients without consent, 4) patients who were not permanently living in Finland, 5) patients on intermediate care and, 6) patients who received RRT for non-renal indications (Figure 2b).

4.3 DATA COLLECTION

In study I, data on the studied drug and its dosing, patient demographics, details of the given RRT treatment, and patient weight to calculate the CRRT dose adjusted for weight were collected. Pharmacokinetic parameters (Vd, T1/2, area under the curve (AUC)), total clearance, CRRT clearance, renal clearance, and sieving/saturation coefficient) and recommendations given for drug dosing were recorded.

The clinical data used in studies II-IV were retrieved from the Finnish Intensive Care Consortium database. The database was originally based for benchmarking purposes. Data on patient APACHE III admission diagnosis,[127] International Classifications of Diseases, 10th revision (ICD-10) diagnosis, demographic data, as well as physiologic and laboratory data needed for calculating the SAPS II,[136] SOFA,[239] and APACHE II[126] severity scores are routinely collected. Additionally, data for the Therapeutic Intervention Scoring System (TISS)[122] are recorded. The data are transferred directly from the ICU clinical information management system to the database, after being validated by trained personnel and filtered for outliers. For studies II and III, the routine data including the demographic data, diagnoses, as well as daily creatinine values were obtained. The SAPS II and SOFA scores, in addition to the physiologic data regarding the first day of ICU treatment, were used. Patients' vital status at hospital discharge and at six months, were obtained from the database.

For study IV, the routine data collection set was expanded to include all physiologic and laboratory data recorded in the clinical information system. Additionally, supplementary data on patients' chronic illnesses, medication, and treatment prior to ICU admission were collected with case report forms. Data on daily fluid balance, characteristics of the given RRT, and patients' sepsis status on days one to five, and data on RRT thereafter twice a week were recorded. Data on patients RRT need at 90 days were collected. Data on patients' vital status at 90 days from the Finnish Population Register Centre were obtained.

4.4 DEFINITIONS

Organ dysfunction (II-IV)

Organ dysfunction was defined as an organ specific SOFA score 3 or 4.[240]

Sepsis (II-IV)

In studies II and III, the presence of sepsis was retrospectively assessed according to the American College of Chest Physicians / Society of Critical Care Medicine criteria.[23] Data on presence of infection were based on patients' APACHE III and ICD-10 diagnosis. Presence of systemic inflammatory response syndrome was screened using physiologic data from the first 24 hours of ICU treatment and organ failures using the first day's SOFA score. In study IV, the presence of severe sepsis was assessed daily from admission to fifth ICU treatment day on the basis of the American College of Chest Physicians / Society of Critical Care Medicine criteria.[23]

Acute kidney injury (II)

The presence of AKI was retrospectively screened according to the creatinine criteria of the RIFLE classification (Table 1).[19] The lowest value of the following: lowest recorded creatinine value during the entire ICU stay or the calculated baseline creatinine, was used as baseline creatinine. The baseline creatinine was calculated using the MDRD equation assuming a GFR of 75 mL/min/1.73m^2 as recommended by Acute Dialysis Quality Initiative.[19]

ICU size and annual case volume (III)

A previous Finnish Intensive Care Consortium classification was used to divide ICUs into small (n=7) and large (n=16).[202] Small ICUs had a referral area under 120 000 inhabitants and/or fewer than six beds. The annual case volume of RRT-treated AKI patients in each ICU (the mean case volume of the two years) was calculated. The ICUs were divided into volume tertiles according to the mean annual case volume; low (n=9, two ICUs had equal annual case volume on the border of low and medium tertile), medium (n=7), and high (n=7).

Fluid overload (IV)

The cumulative fluid balance from ICU admission to RRT initiation (including the day of RRT initiation) was calculated. To define the degree of fluid overload, the cumulative balance in liters was divided by patient's baseline weight and multiplied by 100%. Fluid accumulation of 10% was used as a cut-off to define presence of fluid overload.[25,27]

4.5 OUTCOME MEASURES

Mortality (II-IV)

Data on patients' vital status at hospital discharge and at six months after ICU admission were obtained from the Finnish Intensive Care Consortium database. Data on patients' time of death are registered in the database of the Finnish Population Register Centre and the social security codes of the patients in study IV were used to obtain these data.

Standardized mortality ratio (SMR) (II-IV)

The SAPS II –based SMR was calculated using the expected probability of death calculated from the original SAPS II equation.[136] The sum of observed deaths (O) in a cohort was divided by the sum of the expected deaths (E), which is the SMR of the population (O/E –ratio). A SMR below one means that the observed mortality is lower than what could be expected using the prediction model. Adjusted mortality rates were calculated for patient sub-cohorts in study III by multiplying the SMR in the sub-cohort with the overall mortality of the cohort.

Renal recovery at 90 days (IV)

Renal recovery at 90 days was defined as independence of RRT.[19]

Health-related quality of life (HRQOL) (II)

The HRQOL of all patients admitted to the ICU were assessed at baseline (referring to situation prior to critical illness) and at six months after ICU admission with the EQ-5D instrument[30] as a part of the routine data collection of the Finnish Intensive Care Consortium. Either the patient him-/herself or a proxy answered the questions. At six months, the questionnaire was either performed by phone interview or mailed to the home. The data provider (patient/proxy) was recorded.

The EQ-5D questionnaire[30] (Table 7) consists of five dimensions: 1) mobility, 2) self-care, 3) usual activities (such as work, family or leisure activities), 4) pain/discomfort and, 5) anxiety/depression. Each dimension is scored from 1 to 3. Data on population-based reference values are used to calculate the index score (maximum 1). Additionally, the patient's perception of his/hers current health state is assessed using the visual-analogue scale (VAS) from 0 to 100 (100 representing the best possible health state).[30]

Table 7. The EQ-5D health questionnaire by Brooks et al.[30]

By placing a tick in one box in each group, please indicate which statements best describe your health today.

Mobility

I have no problems in walking about	□
I have some problems in walking about	□
I am confined to bed	□

Self-Care

I have no problems with self -care	□
I have some problems washing or dressing myself	□
I am unable to wash or dress myself	□

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	□
I have some problems with performing my usual activities	□
I am unable to perform my usual activities	□

Pain/Discomfort

I have no pain or discomfort	□
I have moderate pain or discomfort	□
I have extreme pain or discomfort	□

Anxiety/Depression

I am not anxious or depressed	□
I am moderately anxious or depressed	□
I am extremely anxious or depressed	□

4.6 STATISTICAL ANALYSES

Data and statistical tests

The normality of continuous variables was examined with the Kolmogorov-Smirnov test, and as variables were not normally distributed, continuous data were reported as medians with interquartile range (IQR, 25^{th} -75^{th} percentiles) and nominal data as count and percentage. A two-sided P-value <0.05 was considered to be significant. In logistic regression, a P-value <0.05 in studies II-III, and a more strict P-value of <0.01 in study IV, was considered to be significant.

Chi-square test or Fisher's exact test was used, as appropriate, to compare categorical variables. Mann-Whitney U-test was used to compare two, and Kruskal-Wallis to test three, continuous variables. Wilcoxon signed rank test was used to compare repeatedly measured data of HRQOL (II). Kaplan-Meyer survival curves for patients with and without fluid overload were constructed and compared with the log-rank test (IV).

Logistic regression (II-IV)

Binomial logistic regression was used to study factors associated with hospital mortality (II, III) and 90-day mortality (IV). A backwards elimination approach with a significance level of <0.05 for entry and >0.10 for stepwise removal was used. The goodness-of-fit of the model (model calibration) was assessed with Hosmer-Lemeshow statistics. To measure discrimination of the model (the ability of the model to predict the outcome), the correct classification rate was calculated. Additionally, the area under the receiver-operator characteristic curve was calculated for the final model in study IV to measure discrimination.

In the logistic regression models, odds ratios (OR) are routinely used as measures of association. ORs are not equivalent to risk ratios (RR), and the more common the studied outcome is, the more ORs overestimate the RR.[216]

Propensity score (III)

Propensity score is increasingly used in observational studies, where the treatment assignment cannot be controlled.[83] It is used to control for confounding in treatment effect caused by the differences in the treatment assignment.[83] The propensity score is the conditional probability that the study subject receives the treatment in question when all measured confounding factors have been accounted for.[29] A propensity score model to adjust for potential differences in the probability of a patient to receive RRT was generated in study III. Data from patients without (n=19 122) and with RRT (n=1558) were used. Variables found to significantly differ between these patient groups (age, sex, medical admission, elective admission, presence of sepsis, renal and extra-renal SOFA score (on day 1), and SAPS II score without age points) were entered in the logistic regression model, of which a propensity score for each patient to receive RRT was obtained.

5. RESULTS

5.1 QUALITY OF PHARMACOKINETIC STUDIES (I)

The literature search revealed 95 relevant original articles, of which 49 (52%) fulfilled the inclusion criteria. Seven of the included publications were case reports. The 49 publications reported of 64 separate studies that included a median (IQR) number of 6 (4-7) patients. The median (IQR) Downs and Black quality score calculated for the 42 original publications was 15 (14-16) of 32. The median (IQR) total number of reported minimum reporting criteria by Acute Dialysis Quality Initiative in the 49 original articles was 7 (5-8) of 12, and reported operational and patient characteristics was 4 (3-5) and 3 (1-4) of 6. When studies published before and after 2002 were compared in terms of number of reported Acute Dialysis Quality Initiative criteria, no significant improvement was found (P=0.341).

The median (IQR) calculated mean CRRT dose in the 64 separate studies was 22.1 (14.3-27.6) mL/kg/h and the patient count–weighted (n=367) dose 23.7 (18.8-27.9) mL/kg/h. In 32 (50%) studies the calculations were based on measured ultrafiltrate flow. The duration of CRRT was reported in 18 (28%) of the studies. The weighted CRRT dose was significantly higher in studies published after the year 2001 compared to those published before, 24.2 (18.8-27.9) vs. 19.7 (13.5-25.1) mL/kg/h, P=0.033.

5.2 INCIDENCE OF RRT FOR AKI (II, IV)

Between 1 January 2007 and 31 December 2008, 1686 patients received RRT for AKI. The population-based incidence of RRT for AKI (95% CI) was 19.2 (17.9-20.5) per 100 000 per year among ≥ 15 year-old Finnish inhabitants (reference population 4 383 358) (II). When patients under 18 (n=6) were excluded, the incidence (95% CI) among the Finnish adult population was 20.2 (18.8-21.5) per 100 000 per year (reference population 4 182 978) (unpublished data). From 1 September 2011 to 1 February 2012, 296 adults were treated with RRT for AKI, and the population-based incidence (95% CI) was 19.4 (17.2-21.6) per 100 000 adults per year (reference population 3 671 143) (IV). The population-based incidences in studies II and IV, according to hospital districts, are presented in Figure 3. The ICU-incidence (95% CI) of RRT among ≥ 15 year-old general ICU patients was 6.8% (6.5-7.1%) (II).

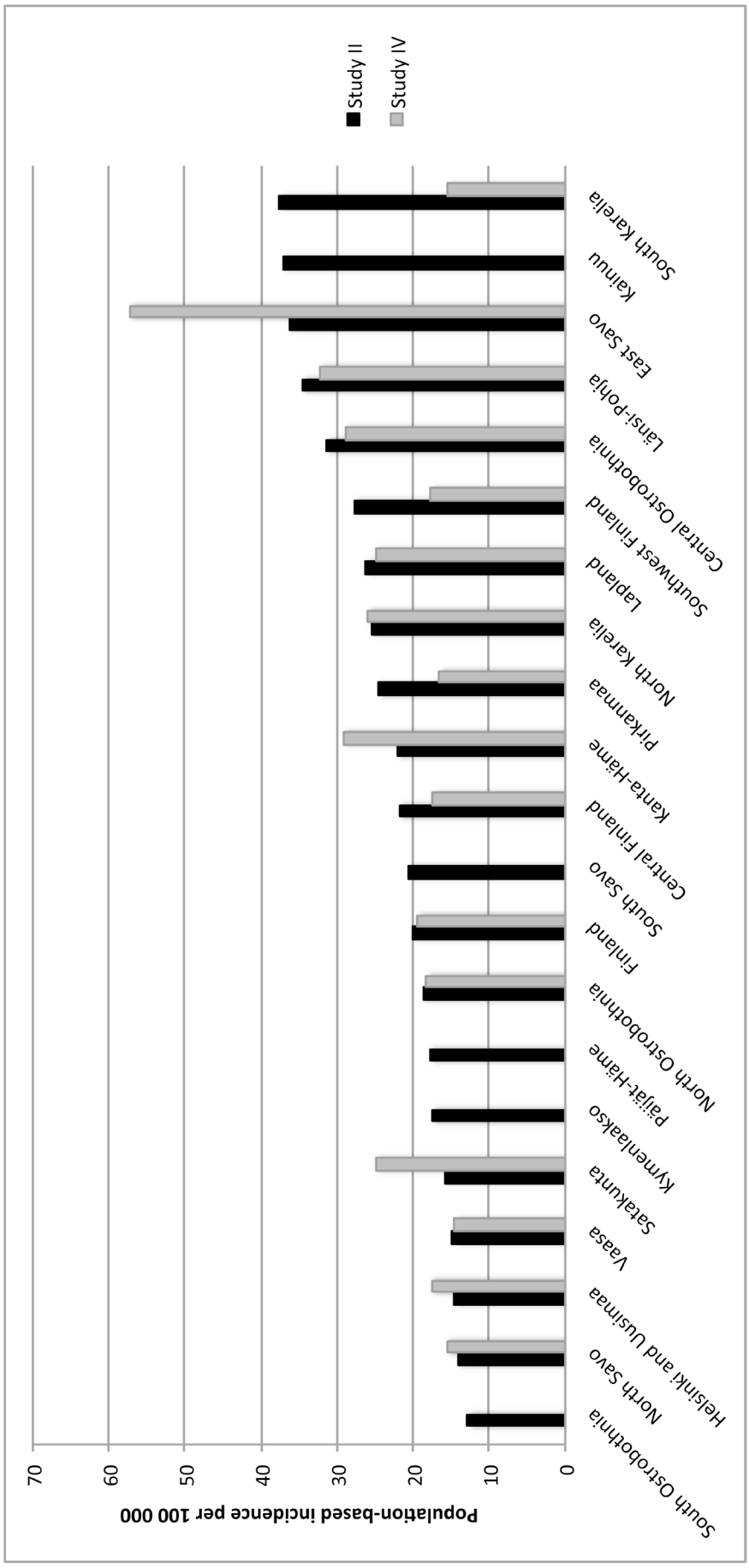

Figure 3. Population-based incidence (per 100 000 adults per year) of RRT for AKI according to hospital district in studies II and IV.

5.3 PATIENT CHARACTERISTICS (II-IV)

When patients in study IV and RRT patients in study II were compared in terms of patient characteristics presented in Table 5, patients in study IV had more frequently surgical admission (P=0.007), higher SAPS II (P=0.009), SOFA (P=0.033), and average TISS scores (P=0.004). The length of hospital stay was longer in study II (P=0.049). No statistically significant differences in other parameters existed. When patients (n=22) treated in the Helsinki University Hospital Cardiac Surgical ICU (not a member of the Finnish Intensive Care Consortium in 2007-2008 and patients not included in study II) were excluded, only differences in the SAPS II score and hospital stay remained significant: The median (IQR) SAPS II score was 48 (37-62) in study II vs. 53 (41-66) in study IV (P=0.001) and hospital stay (days) was 16 (8-29) in study II vs. 14 (5-27) in study IV, (P=0.013). (unpublished data)

5.4 RENAL REPLACEMENT THERAPY (II, IV)

The indications for initiating RRT are presented in Table 8. The median (IQR) number of reported indications was 3 (2-4) (IV). The median (IQR) RRT initiation day was 1 (1-2) in both studies, and did not significantly differ between studies II and IV (P=0.064) (Figure 4).

Table 8. Indications for RRT initiation (IV).

	No./total no. (%)
Oliguria	223/286 (78.0)
High creatinine	196/279 (70.3)
Acidosis	181/278 (65.1)
Fluid accumulation	116/270 (43.0)
Hyperkalemia	72/270 (26.7)
Rhabdomyolysis	34/256 (13.3)
Intoxication	19/265 (7.2)
Other	16/263 (6.1)

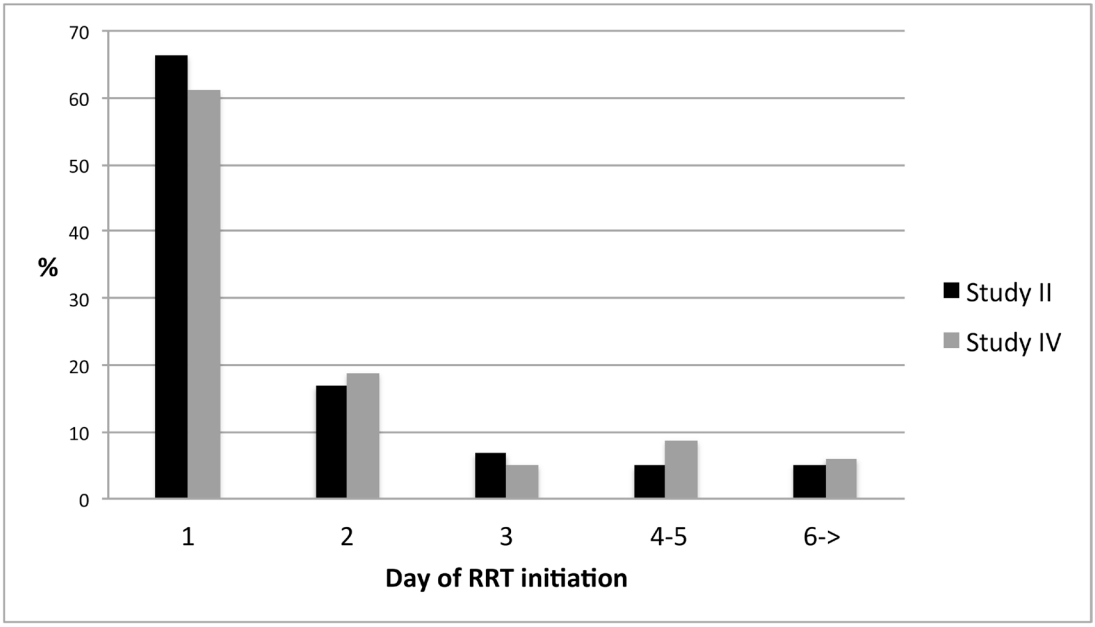

Figure 4. ICU treatment day of RRT initiation in studies II and IV.

The initial RRT modalities in study IV are presented in Table 9 (IV). Of the 215 patients initially receiving CRRT, regional citrate anticoagulation was used in 127 (59.1%), low molecular weight heparins in 61 (28.5%), and unfractionated heparin in 2 (0.9%), and CRRT was initiated without anticoagulation in 25 (11.6%) patients (unpublished data).

The median (IQR) initially prescribed CRRT dose was 35.3 (31.2-40.6) mL/kg/h (Figure 5) (IV). The median (IQR) daily duration recorded in 680 CRRT treatment days was 19 (9.3-24.0) hours, and, thus, the CRRT dose adjusted for duration treatment was 27.9 mL/kg/h. The most common reasons for interruptions in therapy (reported from 137 CRRT treatment days) were circuit clotting in 70 (51.1%), procedure 31 (22.6%), surgery in 19 (13.9%) and technical problems in 17 (12.4%) (unpublished data). The median (IQR) duration of CRRT was 3 (2-6) days (data from 230 patients) and number of IRRT sessions 2 (1-4) (data from 163 patients) (IV).

Table 9. Initial RRT modality (IV).

	Number (%)
Continuous RRT	**215/296 (72.6)**
Continuous venovenous hemodialysis	111 (51.6)
Continuous venovenous hemodiafiltration	93 (43.3)
-predilution	-88 (94.6)
Continuous venovenous hemofiltration	11 (5.1)
-predilution	- 10 (90.9)
Intermittent RRT	**81/296 (27.4)**
Intermittent hemodialysis	62 (76.5)
Sustained low-efficiency dialysis	11 (13.6)
Molecular absorbent recirculating system	4 (4.9)
Other	4 (4.9)

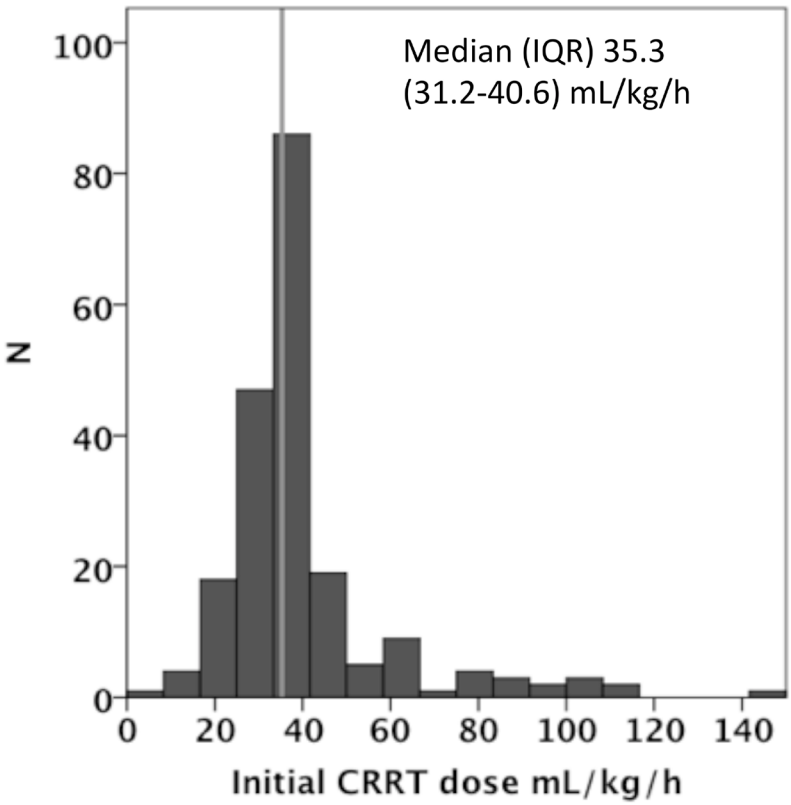

Figure 5. Distribution of the initial prescribed continuous renal replacement therapy (CRRT) dose.

5.5 OUTCOME

5.5.1 MORTALITY (II, IV)

The hospital, 90-day, and six-month mortality rates of patients in studies II and IV are presented in Table 10. Of all 1981 included RRT-treated patients, 685 (34.6%; 95% CI 32.5-36.7%) died in hospital. In study IV, non-survivors were older [median (IQR) age 70 (58-77) vs. 62 (50-69), P<0.001], had higher SAPS II scores [63 (51-77) vs. 46 (36-56), P<0.001], and had severe sepsis more frequently (59.5% vs. 40.6%, P=0.002). A comparison of survivors and non-survivors regarding parameters at RRT initiation is presented in Table 11.

Table 10. Outcome of patients with or without RRT in study II and patients in study IV.

	Study II		**Study IV**
	Non-RRT N=23218	RRT N=1686	RRT N=296
Hospital mortality[a]	3604/23202 15.5% (15.0-16.0%)	589/1685 35.0% (32.7-37.3%)	96/296 32.4% (31.9-32.9%)
90-day mortality			116/296 39.2% (38.6-39.8%)
6-month mortality[a]	5101/18367 27.8% (27.2-28.5%)	699/1415 49.4% (46.8-52.0%)	
SAPS II based SMR – (95% CI)	0.61 (0.59-0.63)	0.76 (0.70-0.82)	0.64 (0.52-0.78)

Mortality rates expressed as number/total number % (95% CI).
SAPS; Simplified Acute Physiology Score, SMR; standardized mortality ratio
[a] Comparison between non-RRT and RRT patients in study II, P<0.001

Table 11. Parameters at RRT initiation compared between survivors and non-survivors (IV).

	Data available	**Survivors (N=180)**	**Non-survivors (N=116)**	**P-value**
SOFA score	290	9 [6-11]	12 [9-14]	<0.001
Renal SOFA score	290	3 [1-4]	4 [2-4]	0.022
Cumulative balance (L)[a]	283	3.1 [0.3-6.4]	6.2 [2.2-9.7]	<0.001
Fluid accumulation (%)[a]	283	3.6 [0.3-8.2]	8.0 [3.0-12.9]	<0.001
Urine output mL/24h	278	510 [157-1701]	150 [35-496]	<0.001
Received diuretics prior to RRT initiation	296	117/180 (65.0%)	85/116 (73.3%)	0.160
Received colloids prior to RRT initiation	290	114/177 (64.4%)	94/113 (83.2%)	<0.001
Creatinine (µmol/L)	290	279 [169-506]	237 [164-336]	0.049
Lactate (mmol/L)	276	1.8 [1.1-4.8]	3.8 [1.7-8.0]	<0.001
pH	291	7.31 [7.20-7.38]	7.25 [7.17-7.37]	0.072
Base excess (mmol/L)	292	-7.6 [-13.0- -3.4]	-10.0 [-13.9- -5-1]	0.046
Time from ICU admission to RRT initiation (hours)	290	10.9 [2.5-42.1]	19.2 [6.3-41.3]	0.044
Continuous RRT as initial modality	296	121/180 (67.2%)	94/116 (81.0%)	0.011

Continuous data expressed as median [IQR] and categorical data as number/total number (%).
SOFA; Simplified Acute Physiology Score
[a] calculated from ICU admission to RRT initiation (including the day of RRT initiation)

5.5.2 RENAL RECOVERY (IV)

Data on RRT need at 90 days were available from 168 survivors, of which 34 (18.9%, 95% CI 13.2-24.6%) were still dependent on RRT. Renal recovery rate seemed higher among patients initially treated with CRRT, 82.3% (93 of 113) compared to 74.5% (41 of 55) with IRRT, but the difference was not statistically significant (P=0.306).

5.5.3 HEALTH-RELATED QUALITY OF LIFE (II)

Of the 716 6-month survivors who received RRT during ICU stay, data regarding HRQOL were available from 313 (44%) patients. Patients without HRQOL data at six months were less severely ill [median (IQR) SAPS II score of 40 (28-50) vs. 45 (35-55), P<0.001], younger [median (IQR) age 59 (47-67) vs. 61 (50-71), P=0.005), had shorter median ICU stay (4.6 (1.6-10.6) vs. 5.9 (2.0 -11.6) days, P=0.045] and were more often admitted electively (12% vs. 6%, P=0.007) than those with data (unpublished data).

RRT patients had significantly lower HRQOL as measured with the EQ-5D index than patients without RRT at six months (Table 12). Patients with RRT had more frequently difficulties in mobility, self-care and usual activities, but regarding bodily pain and anxiety or depression no statistically significant differences were found. According to the VAS, RRT patients perceived their own health status as good as patients without RRT at six months (Table 12).

Table 12. Health-related quality of life in patients according to RRT treatment (II).

	Non-RRT N=23218	**RRT N=1686**	**P-value**
EQ-5D index at baseline – median [IQR] – no./total no. (%)	0.69 (0.53-1.0) 7487 / 13266 (56.4%)	0.68 (0.49-1.0) 431/716 (60.2%)	0.004
EQ-5D index at six months – median [IQR] – no./total no. (%)	0.68 (0.52-1.0) 5415 /13266 (40.8%)	0.63 (0.49-0.79) 313/716 (43.7%)	0.015
VAS at baseline – median [IQR] – no./total no. (%)	70 (50-80) 4505 /13266 (34.0%)	60 (40-80) 223/716 (31.1%)	0.009
VAS at six months – median [IQR] – no./total no. (%)	70 (55-85) 4841/13266 (36.5%)	70 (50-80) 274/716 (38.3%)	0.059

VAS; visual analogue scale

5.6 FACTORS ASSOCIATED WITH OUTCOME

5.6.1 GENERAL (II, IV)

The results of logistic regression models for hospital mortality (II) and 90-day mortality (IV) are summarized in Table 13. SAPS II score (II) and SAPS II score without age points and age as a separate variable (IV) were found to be associated with worse outcome. In study II, the SOFA score did not remain significant in a preliminary model, and was replaced with more organ specific variables. Non-renal SOFA score was significantly associated with an increased risk for mortality in study IV. Presence of severe sepsis was significantly associated with an increased risk for mortality in study II, but not in study IV. Higher creatinine on ICU admission day was associated with a decreased risk for mortality in study II, but creatinine prior to RRT initiation was not significantly associated with an increased risk for mortality in study IV. Longer time from hospital admission to ICU admission was associated with an increased risk for mortality (II). Time from ICU admission to RRT initiation was not significant (IV).

Table 13. Factors significantly associated with outcome in logistic regression.

	Odds ratio (95% confidence interval)	P-value
Study II[a] for hospital mortality		
SAPS II score /point	1.056 (1.048-1.065)	<0.001
Time from hospital admission to ICU admission / day	1.055 (1.029-1.081)	<0.001
Plasma creatinine (µmol/L)[b]	0.998 (0.997-0.999)	<0.001
Presence of severe sepsis	1.467 (1.135-1.894)	0.003
Study IV[c] for 90-day mortality		
SAPS II score without age points /point	1.048 (1.024-1.074)	<0.001
Age (years) /year	1.046 (1.019-1.074)	0.001
Non-renal SOFA score[d] /point	1.218 (1.075-1.380)	0.002
Presence of fluid overload	2.626 (1.301-5.299)	0.007

SAPS; Simplified Acute Physiology Score, SOFA; Sequential Organ Failure Assessment

[a] Number of patients included in the model was 1557. Correct classification rate 72.5%. Hosmer-Lemeshow Chi-square test 5.8, P=0.673. Factors not significant in the model: ventilator treatment, vasoactive use, sex, operative admission.
[b] on ICU admission day
[c] Number of patients included in the model was 242. Correct classification rate 74.5%, Hosmer-Lemeshow chi-square test 8.6, P=0.375. Area under the receiver operator characteristic curve (95% CI) 0.816 (0.767-0.866). Factors not significant in the model: time from ICU admission to RRT initiation (days), initial RRT modality (continuous or intermittent), lactate (mmol/L), base excess (mmol/L), and plasma creatinine (µmol/L) at RRT initiation, cumulative urine output on the day of RRT initiation, colloid use prior to RRT initiation (including data from ICU stay and 48h prior to ICU admission), presence of severe sepsis (yes/no) during the ICU admission.
[d] on day of renal replacement therapy initiation.

5.6.2 ICU SIZE AND ANNUAL CASE VOLUME (III)

Annually, a median (IQR) case volume of patients treated with RRT for AKI was 25 (19-45) per ICU. The annual case volume in small vs. large ICUs and in volume tertiles, as well as the patient characteristics and hospital mortality, are presented in Table 14. Patients in small or low-volume ICUs were older, less severely ill, and received less intensive treatment as measured with the TISS score. Crude hospital mortality was also higher in small vs. large ICUs. After adjusting for age, SAPS II score without age points, average TISS score, and day of RRT initiation, treatment of patients with RRT for AKI in small ICUs was associated with an increased risk for hospital mortality [odds ratio (95% CI) 2.061 (1.496-2.840), P<0.001].

Mortality rates of patients treated in the ICUs classified into tertiles according to the annual case volume are presented in Figure 6. Treatment of patients with RRT for AKI in low-volume ICUs was associated with an increased risk for hospital mortality compared to treatment in high-volume ICUs after adjusting for age, SAPS II score without age points, average TISS score, and day of RRT initiation [OR with 95% CI 1.594 (1.152-2.206), P=0.005]. After the same adjustments, treatment in medium-volume ICUs compared to high-volume ICUs was associated with an odds ratio (95% CI) of 1.377 (1.029-1.844), P=0.032 for increased risk for mortality. Propensity to receive RRT did not remain significant in any of the models investigating association between ICU size or annual case volume and hospital mortality.

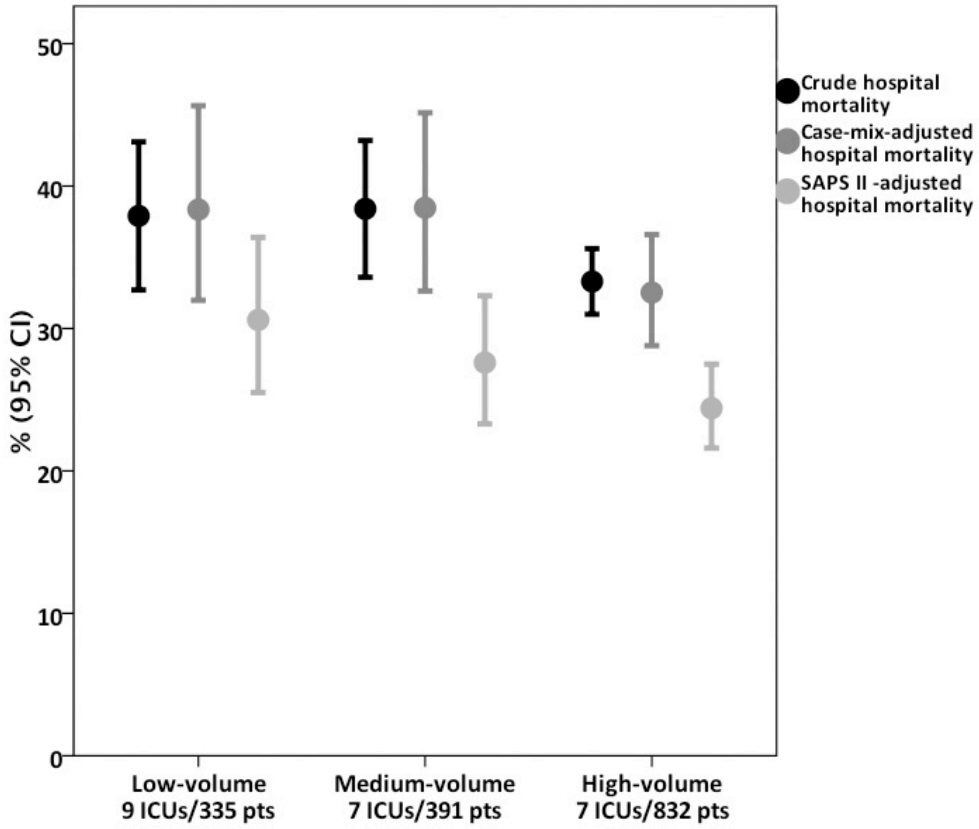

Figure 6. Crude, case-mix-, and SAPS II –adjusted hospital mortality rates (with 95% confidence intervals) in ICUs classified according to annual case volume.

Table 14. Patient characteristics and outcome according to treatment in small vs. large ICUs or in ICUs classified into tertiles according to the annual case volume of patients treated with RRT (III).

	Small central hospitals (N=7)	Large central hospitals and university hospitals (N=16)	P-value[a]	Low (N=9)	Medium (N=7)	High (N=7)	P-value[b]
No. of patients analyzed	288	1270		335	391	832	
All annual ICU admissions	399 [323-461]	575 [501-927]	0.004	461 [362-552]	550 [413-737]	801 [409-1734]	0.125
Annual case volume of RRT patients	18 [17-24]	30 [23-50]	0.026	18 [16-22]	28 [25-30]	54 [45-77]	<0.001
Age (yr)	66 [57-76]	62 [51-72]	<0.001	65 [54-75]	64 [53-73]	62 [50-71]	<0.001
Male gender	193 (67.0%)	866 (68.2%)	0.726	226 (67.5%)	276 (70.6%)	557 (67.0%)	0.447
Surgical admission	46 (16.0%)	252 (19.9%)	0.136	79 (23.6%)	64 (16.4%)	155 (18.6%)	0.043
Elective admission	18 (6.2%)	39 (3.1%)	0.014	25 (7.5%)	8 (2.0%)	24 (2.9%)	<0.001
SAPS II score	45 [35-62]	50 [40-63]	0.002	46 [35-62]	50 [40-64]	50 [39-63]	0.021
SAPS II score without age points	34 [21-49]	40 [29-53]	<0.001	35 [25-50]	40 [29-54]	40 [29-52]	0.001
SOFA non-renal score (1.day)	6 [3-8]	8 [5-11]	<0.001	7 [4-9]	8 [4-10]	8 [5-11]	<0.001
SOFA renal score (1.day)	3 [1-4]	3 [1-4]	0.162	2 [0-4]	3 [1-4]	3 [1-4]	0.001
Average TISS score	32 [24-39]	37 [30-44]	<0.001	34 [28-41]	35 [30-41]	37 [30-45]	<0.001
RRT initiation on first ICU day	184 (64%)	836 (66%)	0.532	196 (59%)	253 (65%)	571 (69%)	0.004
ICU stay (days)	4.8 [1.0-11.3]	5.5 [2.1-10.8]	0.014	5.9 [1.8-12.1]	5.4 [2.1-11.2]	5.0 [1.9-10.1]	0.218
Hospital stay (days)	17.1 [9.0-29.0]	16.0 [8.0-29.0]	0.150	15.0 [9.0-28.0]	17.9 [9.0-30.1]	15.0 [7.1-29.0]	0.119
Crude hospital mortality -number [% (95% CI)]	120 [41.7% (36.0-47.4%)]	434 [34.2% (31.6-36.8%)]	0.017	127 [37.9% (32.7- 43.1%)]	150 [38.4% (33.6- 43.2%)]	277 [33.3% (31.0- 35.6%)]	0.134
SAPS II SMR – (95% CI)	0.97 (0.80-1.15)	0.70 (0.63-0.77)		0.86 (0.72-1.02)	0.78 (0.66-0.91)	0.68 (0.61-0.77)	

Continuous data expressed as median [IQR] and categorical data as number (%).

SAPS II; Simplified Acute Physiology Score, SOFA; Sequential organ Failure Assessment, TISS; Therapeutic Intervention Scoring System, SMR; standardized mortality ratio

[a] Comparison between small and large ICUs; [b] Comparison between low-, medium-, and high-volume ICUs

5.6.3 FLUID OVERLOAD (IV)

Of 283 patients with complete data on fluid balance, 76 (26.9%) had fluid overload at RRT initiation. Patients with fluid overload, compared to those without, had higher SAPS II score [median (IQR) 55 (44-77) vs. 50 (40-63), P<0.001], experienced severe sepsis more often (64.5% vs. 42.5%, P=0.001), and had lower urine output on the day of RRT initiation [median (IQR) 164 (35-511) mL vs. 429 (110-1531) mL, P<0.001]. They also reported a longer median (IQR) time from ICU admission to RRT initiation, 26.9 (10.7-43.7) h vs. 9.3 (2.5-35.7) h, P<0.001 and had CRRT as an initial modality more frequently (92.1% vs. 66.7%, P<0.001). Patients with fluid overload had significantly higher crude 90-day mortality compared to those without, 59.2% (45 of 76) vs. 31.4% (65 of 207), P<0.001. After adjustments, fluid overload at RRT initiation remained significantly associated with increased risk for 90-day mortality (Table 13).

6. DISCUSSION

6.1 QUALITY OF PHARMACOKINETIC STUDIES

In the systematic review regarding the quality of published pharmacokinetic studies in CRRT patients, the general quality of the included studies was moderate, while the reporting of the characteristics of the CRRT treatment, as recommended by Acute Dialysis Quality Initiative,[124] was poor. Almost half of the relevant original articles found in the literature search had to be excluded because of the inadequate reporting of CRRT parameters. The study inclusion criteria comprised one to three of the CRRT characteristics, which caused selection bias. None of the included studies reported the CRRT dose standardized to patient weight. Some studies standardized the effluent flow rates, which, however, does not account for the patient size. Regarding patient characteristics, half of the studies failed to report a disease severity score, which impairs the ability to generalize from those studies. No improvement in reporting these parameters after the publication of the Acute Dialysis Quality Initiative minimal reporting criteria was detected. Correspondingly, regarding the reporting of cluster randomized trials, the penetration of published recommendations have been observed to be inadequate.[108] Our findings about inadequate reporting are in line with another systematic review.[141]

The calculated CRRT dose used in the included studies was in line with the current recommendations.[114,120, 114,235] However, only a third of the studies reported the daily duration of CRRT treatment, and as delivered dose may be 20-30% less than prescribed due to interruptions,[187,204,236,237] it is likely that calculations in this study overestimated the true delivered dose. Moreover, prescribing a dose of 25-30 mL/kg/h to compensate for interruptions is recommended,[114, 120, 114,235] and in only a third of the included studies the calculated dose exceeded 25 mL/kg/h.

Recently, in a study where drug dosing was not standardized but the treating clinician was responsible for the empirical drug dosing strategy, no differences were found in the concentrations of several antibiotics in patients receiving CRRT either 25 mL/kg/h or 40 mL/kg/h.[207] This work also demonstrated that the antibiotic concentrations did not reach the target 25% of time, possibly because of the wide range of empirical drug dosing strategies used or variations in other properties affecting drug clearance such as residual renal clearance.[207] Moreover, the measured urea clearance has been reported to be 25-35% less than the estimated urea clearance regarding doses 30-35 mL/kg/h.[52,150] Regarding lower doses of 20-25 ml/kg/h, the reduction in the estimated clearance has been lower.[150] Thus, measuring urea clearance, for example, to give an estimate of true small solute clearance, in addition to reporting and standardizing the CRRT dose, would add value to the mainly well-recorded pharmacokinetic data. However, an individualized drug dosing strategy might be the best way to tackle the complexities in drug dosing during CRRT.[44]

No other studies have screened the completeness of the minimal reporting criteria recorded for CRRT studies by Acute Dialysis Quality Initiative.[124] Given the inadequate

reporting of these criteria in pharmacokinetic studies, in which standardized dosing of both the drug and the CRRT treatment should be self-evident, the reporting may be even more insufficient in other observational studies regarding CRRT. In study IV, data were recorded for all six criteria about patient characteristics, but failed to record data on vascular access, delivery device, and dialysis or replacement fluid composition required in the operational criteria. However, patients receiving IRRT were also included, and data regarding delivery device or used dialysate fluid could be obtained from the manufacturer.

6.2 INCIDENCE OF RRT FOR AKI

The population-based incidence found in studies II and IV was 19.4 - 20.2 per 100 000 adults per year and within the wide range of reports from other regions, where the incidence rate has varied from 4[242] to 96[36] per 100 000 per year. In a study by Cartin-Ceba et al.[36] the incidence of not only RRT but also other ICU syndromes was exceptionally high, possibly because of a liberal ICU admission policy. Older studies have reported lower incidence rates from 4 to 8 per 100 000,[128,221, 242] and a rising trend in the incidence has been found.[242] Compared to a Finnish single-center study conducted in 1992-1993,[128] the population-based incidence in Finland has increased. More recent studies have reported incidence rates from 13.3 to 28.6.[164, 200,253] A study by Prescott et al.[200] also included patients treated outside the ICU. The proportion of ICU patients treated with RRT for AKI in study II corresponded to other reports where 3 to 8% of general ICU patients have received RRT.[12,55,105,165,196,231] The ICU incidence rate is, however, more prone to variations than population-based incidence, since the denominator depends on the admission policy of the ICU.

The population-based incidence in Finnish hospital districts in study IV corresponded mainly to the findings of study II. In study II, the population-based incidence was three times as high in the hospital district with the highest incidence rate compared to the district with the lowest rate. The hospital districts with higher incidence rates had small central hospitals, and it is possible that indications for RRT as well as ICU admission policies may be different from that of university hospitals and larger central hospitals. Greater variations in the population-based incidence in smaller hospital districts were also found in study IV. This finding may also be due to the shorter study period of study IV compared to study II.

6.3 RENAL REPLACEMENT THERAPY

In study IV, a median of three indications for initiating RRT was reported. The more indications for RRT are present, the higher the mortality has been shown to be.[16] As in the multinational BEST study,[230] the most common indications were oliguria, high creatinine, metabolic acidosis, and fluid accumulation. Hyperkalemia was reported more frequently than in other studies.[204,230]

RRT was initiated early in both studies II and IV. The median time from ICU admission to RRT initiation was one day, and 61-66% of patients had RRT initiated within the first 24 hours of ICU treatment. Few observational studies have reported as early initiation in terms of time from ICU admission.[15,16] In the BEST study,[15] the median time to RRT initiation in days was corresponding to that described here, but only half of the patients were initiated on RRT within the first ICU treatment day. In the study by Bagshaw et al.,[16] the median renal SOFA score at RRT initiation was 4 compared to 3 in study IV; median urine output was slightly less and serum creatinine higher at RRT initiation than in the present study. This finding could imply that RRT was initiated earlier in our study in terms of development of AKI. However, in the study by Bagshaw et al.,[16] only 30% of the patients had received diuretics prior to RRT initiation compared to almost 70% in the present study, which may cause bias in assessing the urine output. In most other reports, RRT has been initiated much later, a median of two to seven days from ICU admission.[204, 143,151 187]

CRRT was the initial modality in 73% of patients in study IV as in several other studies.[16,143,253] In the BEST study,[15] and in a Swedish retrospective cohort study,[18] about 85% of patients have received CRRT, while studies from the U.S. have reported lower proportions of 45-56%.[36, 163] CVVHD and CVVHDF were the mostly used CRRT modalities. Regional citrate anticoagulation was used in 60% of patients receiving CRRT. In the BEST study conducted in 2000, citrate was used in only 10% of patients,[230] which may be because regional citrate anticoagulation was introduced rather recently.[162] However, by 2011, it seems to have been well implemented into clinical practice at least in Finland.

The median daily duration of CRRT treatment in this study was 19 hours, somewhat lower than reported in a RCT,[187] whilst the prescribed CRRT dose was higher than the dose of 20 mL/kg/h reported in the BEST study.[230] The prescribed dose in the present study was slightly higher than the current recommendation of prescribing a dose of 25-30 mL/kg/h to target a delivered dose of 20-25 mL/kg/h.[120] However, after adjusting for treatment interruptions, the median CRRT dose was 28 mL/kg/h, in line with the current recommendations.[120]

6.4 OUTCOME

6.4.1 MORTALITY

The hospital mortality rates observed in studies II and IV were high among ICU patients in general, but lower than in previous studies with RRT patients with corresponding patient characteristics and disease severity.[67,165,179,230] Both 90-day mortality and 6-month mortality rates were lower than in previous reports.[18,128,204,143,200] Several studies with markedly higher disease severity have reported higher mortality rates in hospital,[184] at 90 days,[59,241] and at 6 months.[59] The SAPS II -based SMR of 0.64-0.76 showed that mortality rates were lower than would be expected based on the SAPS II prediction model. The hospital mortality observed

among patients with RRT was higher than in a previous Finnish study among patients with severe sepsis,[117] while the 90-day mortality was corresponding to Finnish patients with acute lung injury or acute respiratory distress syndrome.[144] In general, disease severity was found to be associated with hospital or 90-day mortality in studies II and IV. The significance of other factors (e.g. creatinine prior to RRT) depends a great deal on the strength of other factors entered in the logistic regression model.

Several potential explanatory factors for the observed better outcome exist. The outcome of all ICU patients treated in Finland has been shown to be rather good, and to improve over time.[203] The SAPS II –based SMR in 2005-2008 among all Finnish ICU patients was 0.64,[203] corresponding to the SMR calculated in the study IV for RRT patients only. Patient characteristics were corresponding in studies II and IV (after excluding the patients treated in the cardiac surgical ICU in study IV) and the timing of RRT did not differ between these studies. Thus, data on RRT dose and modality from study IV are likely to also apply to study II, given that large changes in treatment practices over few years are unlikely. The CRRT dose employed in study IV was according to recommendations, in contrast to, the BEST study for example, where the observed CRRT dose was lower than recommended.[230] RRT was also initiated early, within a median of one day from ICU admission. In studies that have reported a corresponding median time from ICU admission to RRT initiation, the hospital mortality rates were 62% despite corresponding SAPS II and SOFA scores[15] and 52% with slightly higher SOFA scores on the day of RRT initiation[16] than in the study IV. In the study by Bagshaw et al.[16] the used CRRT dose was not reported.

Very early initiation of RRT could possibly mean that some patients who would recover without RRT if a "wait and see" -approach would be used are initiated on RRT unnecessarily.[180] A study including patients with RIFLE-Failure AKI who did not receive RRT showed that the mortality and disease severity of these patients were lower than that of RIFLE-Failure patients with RRT.[217] Regarding our study, the disease severity was comparable with other reports, patients had a median three indications for RRT, and the population-based incidence was in line with other reports. Thus, the timing of RRT in our study is unlikely to be too early.

6.4.2 RENAL RECOVERY

Of 90-day survivors in study IV, only 81% recovered to be independent of RRT at 90 days. Renal recovery rate at 90 days has been reported to vary from 75% to 96%.[18,204,143,164,211] The recovery rate in this study is thus among the lowest, possibly because of the lower mortality rate, and more surviving patients. Furthermore, the proportion of patients receiving IRRT was higher. The use of CRRT has been linked with better renal recovery,[18] whilst the non-recovery of renal function increases the costs of treatment.[157]

6.4.3 HEALTH-RELATED QUALITY OF LIFE

Among cancer patients, a clinically significant difference in the EQ-5D score has been reported to be 0.06-0.08 and 7 in VAS.[198] According to these criteria, no clinically significant difference in HRQOL measured with the EQ-5D index at six months in patients with and without RRT was observed in study II. Of the five dimensions of the EQ-5D index, patients with RRT had slightly lower scores for dimensions of physical health, but no significant differences regarding mental health were observed. A previous study supports these findings.[59] A lower HRQOL among RRT patients compared to matched general population has been reported, but the HRQOL of patients with RRT was not compared to ICU patients without RRT.[59,258] One study using the health utilities index found an extremely low HRQOL in a quarter of patients with RRT, corresponding to a situation equal or worse than death in the general population.[112] This finding is in contrast to the results of other studies that have found RRT patients to be willing to undergo the same treatment again if necessary.[59,90] Moreover, in the present study, RRT patients' perception of their own health according to the VAS corresponded to the perception of patients without RRT and the previously reported values of the general population.[258]

6.5 ASSOCIATION OF ICU SIZE AND ANNUAL CASE VOLUME WITH OUTCOME

The crude mortality of patients treated in large ICUs was lower compared to small ICUs. The difference remained after adjusting for age, disease severity, intensity of treatment, and day of RRT initiation. Patients in small ICUs receiving RRT were older but less severely ill, implying potential differences in indications for RRT. To control for the potential differences in assigning patients to RRT, a propensity score was generated, which did not remain significant in any of the logistic regression models. Organizational factors have been described as one traditional explanation for the volume-outcome effect.[115] They may partly account for the observed difference in outcome in the small vs. large ICUs. Small ICUs in small hospitals may have more limited resources for out-of-office hour surgical expertise and radiological procedures, for example.

The median annual case volume of 25 patients receiving RRT for AKI in all ICUs that was observed in this study was rather low. Other reports regarding annual volume of RRT-treated patients are few, however. Nguyen et al.[174] reported a median annual case volume of 29 in a French cohort and only 17 in a U.S. cohort. The annual case volumes of RRT treated patients both in the present study and in the study of Nguyen and colleagues are much lower compared, for example, to a study regarding volume outcome effect in patients receiving mechanical ventilation.[116]

After adjusting for disease severity, patient age, intensity of care, and time of RRT initiation, treatment in low- or medium annual case volume ICUs was associated with increased risk for hospital mortality compared to treatment in high volume ICUs. This finding is in contrast to the study by Nguyen et al.,[174] where two large cohorts were

divided into quartiles, and no association between annual case volume and outcome was found after adjusting for disease severity, admission diagnosis, time in hospital preceding ICU admission and ICU characteristics. Notably, they had a long study period of ten years which was not adjusted for, and as treatment results of ICU care have been shown to improve over time[203] and mortality of AKI to decrease[11] the long study period may have influenced the results of their study. In contrast,[174] ICUs in the present study were unselected and the findings are in line with those from other ICU patient groups demonstrating the presence of a likely volume-outcome effect.[116,192,257]

6.6 ASSOCIATION OF FLUID OVERLOAD WITH OUTCOME

Patients with fluid overload at RRT initiation had almost twice as high crude 90-day mortality compared to those without. The difference remained after adjusting for age, disease severity, initial RRT modality, presence of severe sepsis, time from ICU admission to RRT initiation, and several other factors. In critically ill children, a strong association between fluid overload at RRT initiation and increased mortality has been shown.[89,227] Among adult patients, fluid accumulation of 5% calculated from 24h preceding RRT initiation[16] or 10% three days preceding a nephrologist consultation (time from consultation to RRT initiation not defined)[25] have been associated with increased mortality. A small prospective study[82] and a retrospective study that also included patients treated outside the ICU,[99] have used weight gain from baseline (preceding critical illness) to RRT initiation to define fluid overload and have reported corresponding results. Additionally, more positive mean daily fluid balance after RRT initiation has been associated with increased mortality.[205]

More severely ill patients typically require larger amounts of fluid in the initial resuscitation phase of critical illness. A higher degree of fluid accumulation at RRT initiation might reflect the overall severity of illness, and fluid balance has been proposed as a biomarker of critical illness.[9] In the present study, patients with fluid overload had higher SAPS II and SOFA scores, had severe sepsis more often, higher lactate values, and lower urine output prior to RRT initiation compared to those without. The association of fluid overload with increased risk for mortality remained, however, after adjusting for all these parameters, and, consequently, severity of illness is unlikely to solely account for these findings. On the other hand, RRT was initiated later among patients with fluid overload, meaning that they had more time to accumulate fluid, but again, the difference in outcome remained after adjusting for time of RRT initiation. Earlier RRT initiation in terms of time, and thus probably also with a lower degree of fluid accumulation, might have altered the outcome of these patients. A threshold value of 10% fluid overload for the use of diuretics or RRT initiation after initial resuscitation phase is included in the current recommendations for management of septic shock in children, if native urine output is not sufficient to maintain fluid balance.[27]

6.7 LIMITATIONS

Several limitations in these studies should be addressed. In study I, assumptions regarding patients' fluid balance or hematocrit had to be made in a third of the included studies to calculate the CRRT dose. Missing data, varying patient characteristics, and differences in the provided CRRT made statistical comparison of the included studies impossible.

Regarding studies II-IV, inherent limitations of observational studies apply. The observed associations do not prove causality. Moreover, although a number of factors in each study were adjusted for, it may be possible that something that was not measured affected outcome. Hospital mortality used as an endpoint in the logistic regression models in studies II and III is not a recommended endpoint,[88] however, the results of study III were robust for sensitivity analysis performed by excluding patients discharged to other ICUs. In study IV, a fixed endpoint at 90 days was used as recommended.[88] The retrospective design of studies II and III is a further limitation, however, the used dataset was comprised of prospectively recorded data.

In studies II and IV, data on RRT administered outside ICUs were not included. However, RRT for AKI outside ICUs in Finland is uncommon, and thus the bias caused by this in the population-based incidence is only minor. Regrettably, data on HRQOL were available for only 44% of six-month-survivors with RRT during their ICU stay, which may have caused bias in study II. The respondents were older, were admitted due to emergency more often, and had higher disease severity and a longer ICU stay compared to the non-respondents. Given that the patients lost to follow-up were less severely ill, the potential bias due to the low-response rate is likely to cause underestimation of HRQOL rather than overestimation.

Since the data in studies II and III were part of the routine dataset recorded of all ICU patients, data regarding RRT indications, dose, and modality could not be obtained. However, as the characteristics of the RRT patients in studies II and IV were much alike, and treatment practices are unlikely to largely evolve in a few years, results regarding the provided RRT in study IV could also be applied in studies II and III.

In study III, differences in the ICU admission and treatment restriction policies may account for the observed differences in part. Furthermore, the study was probably underpowered to detect a volume-outcome effect in the crude mortality also between the ICU volume tertiles. Due to the small population of Finland, the referral populations and bed numbers of Finnish ICUs are small compared to other, more densely populated countries. However, the results of this study are applicable to other small countries with small ICUs.

Finally, the power of study IV was insufficient to assess factors associated with the non-recovery of renal function at 90 days. Moreover, data on the fluid balance preceding ICU admission could not be recorded, however, unlike some previous studies,[16,25] cumulative balance right from ICU admission to RRT initiation was assessed.

6.8 CLINICAL IMPLICATIONS

These data may have following clinical implications:

Pronounced interpatient differences in the included studies about pharmacokinetics during CRRT allowed neither the provision of new recommendations about drug dosing nor statistical comparisons between the studies. Thus, to guide drug dosing in CRRT-receiving patients, either data and recommendations from those included studies with adequate reporting and quality or a recently published individualized drug dosing regimen[44] could be used.

The incidence rate of RRT-treated AKI in the ICU can be used to plan future studies and resource allocation. Given the observed increasing trend in the population-based incidence and the aging of the population, the need for RRT is also likely to increase in the future.

Despite a high mortality rate compared to other patient groups treated in the ICU, the outcome of RRT-treated patients observed in this study was rather good relative to other studies. Moreover, as the HRQOL of RRT patients did not clinically differ from those without RRT and patients themselves perceived their HRQOL to be rather good at six months, treating these critically ill patients with RRT seems to be worthwhile. However, the cost-effectiveness of the treatment needs to be evaluated.

RRT patients treated in large central and university hospitals had lower crude and adjusted mortality rates than patients treated in small central hospitals. If the reasons for this finding could be elucidated in-depth and the results confirmed in other studies, treatment of these patients or certain subgroups might be reasonable to concentrate to larger centers.

The association of fluid overload at RRT initiation and worse outcome requires confirmation in further studies. Fluid accumulation is potentially modifiable in many patients, either initiating RRT before it develops, or using a more restrictive fluid management strategy. Thus, RRT initiation before fluid overload might alter the outcome.

6.9 FUTURE PERSPECTIVES

Only during the last decade, a reliable and validated definition of AKI has been established,[19,160] with a recent update[120] thus enabling inter-study comparisons and enhancing the validity of research. RRT has largely evolved as well, and knowledge of the best ways to provide RRT have markedly increased regarding adequate modality[241] and dose of CRRT.[204,187] The care of this severely ill and heterogeneous group of AKI patients requiring RRT is complex, and much remains to be elucidated, however. As RRT itself is not a cure for AKI but a supportive treatment, gathering data regarding underlying reasons for AKI, and finding measures to prevent and treat these reasons, is of utmost importance. Recently, the concept of "permissive hypofiltration" was introduced.[38] Its aim is to allow the injured kidney rest by initiating RRT early, instead of increasing its work load with fluid challenges.[38]

In this study, RRT was found to be provided according to current international recommendations nationwide, but it is likely that some regional variations in practices still exist. Furthermore, variations in the population-based incidence in different hospital districts were found. Thus, the practices in different Finnish ICUs should be studied in more detail. Uniform criteria for RRT initiation in Finnish ICUs should be proposed.

Early initiation of RRT in terms of time from ICU admission may be one possible explanation for the rather good outcome in this study. Thus far, good-quality data on timing of RRT are sparse, reflected by the inability of an international consensus committee to provide a graded recommendation on RRT timing.[120] A multinational RCT would be needed to adequately assess the timing of RRT and outcome.[120] Meanwhile, a prognostic model for the need for RRT could be developed, including physiologic data on ICU admission, underlying co-morbidities, admission diagnosis, and several new biomarkers, e.g. NGAL. A reliable prediction model for the need for RRT would provide more tools for clinicians to initiate RRT early. Moreover, the ability of novel biomarkers to predict 90-day mortality of RRT patients in general, and in subgroups such as severe sepsis, could be evaluated. Regional citrate-calcium anticoagulation was widely used in the Finnish ICUs, and its possible favorable effect on outcome[181] warrants further investigation.

The renal recovery rate found in this study was somewhat lower than in several other reports. Future studies should address the reasons for this finding, and subsequently, potential solutions. The kidney function of those patients who received RRT during their ICU stay but initially recovered independent of RRT has been shown to deteriorate over time more often than in patients not treated with RRT in the ICU.[245] To diagnose the deteriorating kidney function of those patients with an initial renal recovery, a routine clinical long-term follow-up should be implemented in the care of these patients. The non-recovery of kidney function causes increased costs.[157] Thus, for a comprehensive analysis of the cost-effectiveness of RRT treatment, a long-term follow-up of these patients, including assessment of renal function and HRQOL, is

needed. A national registry including all patients treated with RRT in the ICU would facilitate the analysis of the cost-effectiveness.

Results regarding presence of fluid overload at RRT initiation and its association with increased risk for mortality are in line with several previous studies.[16,25,89,227] As these all are observational studies, no causality with fluid overload and increased mortality has been shown. To confirm the association of fluid overload with increased risk for mortality, a multicenter RCT would be needed. It could also shed light into whether fluid overload itself causes AKI or solely reflects the severity of illness. Threshold values for degree of fluid accumulation as triggers for RRT initiation should be evaluated as well.

Finding answers in the genetics for susceptibility to develop AKI, the need for RRT, and renal recovery thereafter is a long-term goal in the field of AKI research. Indeed, a genetic susceptibility related to the presence of certain HLA alleles for decreased need for RRT in the presence of AKI was recently described.[190]

7. CONCLUSIONS

The following conclusions can be drawn on the basis of these studies:

1. The general quality of pharmacokinetic studies on CRRT-receiving patients measured with the Downs and Black quality score was moderate. The reporting of CRRT and patient characteristics was poor, while the retrospectively calculated CRRT dose used in these studies was according to the recommendations.

2. The population-based incidence of RRT for AKI was 19.4 - 20.2 per 100 000 adults per year, broadly in line with studies conducted in other regions.

3. RRT was initiated early compared to other reports, after a median of 14 hours from ICU admission. A median of three indications were present at RRT initiation, the most common being oliguria or anuria, high creatinine, and acidosis. In 73% of patients, the initial RRT modality was continuous. The CRRT dose adjusted for daily duration of treatment was according to current recommendations.

4. The short-term and long-term mortality rates of patients receiving RRT were lower than previously reported. Patients treated in small ICUs had higher crude and adjusted hospital mortality rates compared to those treated in large ICUs. Patients with fluid overload at RRT initiation had twice as high crude 90-day mortality rate than patients without fluid overload, and the difference remained after adjusting for patient age, severity of illness, presence of sepsis, time from ICU admission to RRT initiation, and initial RRT modality.

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